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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant	: Rubino, et al.	
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TC/A.U.	: 1614	
Examiner	: Polansky, G.	
Title	: PARENTERAL FORMULATIONS	

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SEVENTH INFORMATION DISCLOSURE STATEMENT

Sir:

Applicants submit to the Examiner the attached document listing and this paper pursuant to 37 CFR §1.56 and §§1.97-1.98.

This Information Disclosure Statement is submitted concurrently with a Request for Continued Examination and corresponding fee. Therefore, no additional fees are believed due in connection with this paper.

REMARKS

Listed below and attached are copies of 2 oppositions filed in the corresponding European Patent No. 1 553 940.

- Opposition by Opponent Dr. Hendrik Wichmann ("Wichmann Opposition")
- Opposition by Opponent Teva Pharmaceutical Industries Ltd. ("Teva Opposition")

Listed below are the documents cited in the Wichmann Opposition.

- US Patent Application No. 60/399,526
- International Patent Publication No. WO 01/97809
- US Patent No. 5,530,006
- US Patent No. 5,516,770
- US Patent No. 5,616,588
- FIEDLER, H. *Lexikon der Hilfsstoffe fur Pharmazie, Kosmetik und angrenzende Gebiete,* vol. 2, no. 4, Auglage, pp. 1210-1217, Cantor-Verlag, Aulendorf, Deutchland, 1996.
- Great Britain Patent No. GB 2 327 611
- US Patent No. 4,401,653
- PODSYPANINA, K, An inhibitor of mTOR reduces neoplasia and normalizes p70/S6 kinase activity in Pten$^{+/-}$ mice, PNAS, vol. 98, no. 18, pp. 10320-10325, August 2001.
- International Patent Publication No. WO 94/02136
- SWEETANA, S. AND AKERS, M., Solubility principles and practices for parenteral drug dosage form development, PDA Journal of Pharmaceutical Science and Technology, vol. 50, no. 5, pp. 330-342, September 1996.

- STRICKLEY, R., Parenteral forumulations of small molecules therapeutics marketed in the United States (1999) Part I, Journal of Pharmaceutical Science and Technology, vol. 53, no. 6, pp. 324-349, November 1999.
- POWELL, M., Compendium of Excipients for Parenteral Formulations, PDA Journal of Pharmaceutical Science and Technology, vol. 52, no. 5, pp. 238-311, November 1999.
- SORBERA, L.A., et al, CCI-779 Oncolytic mTOR inhibitor, Drugs of the Future, vol. 27, no. 1, pp. 7-13, January 2002.
- Wyeth Pharmaceuticals Inc, HIGHLIGHTS OF PRESCRIBING INFORMATION, (Torisel, temsirolimus), Philadelphia, USA, May 2007.
- German Patent No. DE 44 18 115
- GARBER, K., Rapamycin's Resurrection: A new way to target the cancer cell cycle, J. National Cancer Institute, vol. 93, no. 20, pp. 1517-1519, October 2001.
- GRUNWALD, V., et al, Inhibitors of mTOR reverse doxorubicin resistance conferred by PTEN status in prostate cancer cells, Cancer Research, vol. 62, pp. 6141-6145, November 2002.
- International Patent Publication No. WO 2000/33878.

Listed below are the documents cited in the Teva Opposition.

- International Patent Publication No. WO 01/97809
- PODSYPANINA, K, An inhibitor of mTOR reduces neoplasia and normalizes p70/S6 kinase activity in Pten$^{+/-}$ mice, PNAS, vol. 98, no. 18, pp. 10320-10325, August 2001.
- DUDKIN, Biochemical correlates of mTOR inhibition by the rapamycin ester CCI-779 and tumor growth inhibition, Clinical Cancer Research, vol. 7, pp. 1758-1764, June 2001.

- GEORGER, Antitumor activity of the rapamycin analog CCI-779 in human primitive neuroectodermal tumor/medulloblastoma models as single agent and in combination therapy, Cancer Research, vol. 61, pp. 1527-1532, February 2001.
- "Solution Formulations" in Pharmaceutical Preformulation and Formulation, 2001, pp. 196-210.
- MENDENHALL, Stability of Parenterals, Drug Development and Industrial Pharmacy, vol. 10, no. 8-9, pp. 1297-1342, October 1984.
- Great Britain Patent No. GB 2 327 611
- US Patent No. 5,530,006
- YU, mTOR, a novel target in breast cancer: the effect of CCI-779, an mTOR inhibitor, in preclinical models of breast cancer, Endocrine-Related Cancer, vol. 8, pp. 249-258, September 2001.
- GRUNWALD, V., et al, Inhibitors of mTOR reverse doxorubicin resistance conferred by PTEN status in prostate cancer cells, Cancer Research, vol. 62, pp. 6141-6145, November 2002.
- US Patent No. 5,516,770

In addition, the documents cited in the Oppositions are listed on the enclosed forms, to the extent that they were not cited in one or more previous Information Disclosure Statements.

Also attached is the agent's translation of an Office Action issued in corresponding Japanese Patent Application No. 2004-524806. The following documents were cited in the Office Action. Each Japanese patent publication corresponds to the US or International patent publication listed next to it. The documents cited in the office action, including the US and International patent publications corresponding to the Japanese patent publications, are also listed on the enclosed forms, to the extent that they were not cited in one or more previous Information Disclosure Statements.

- PODSYPANINA, K, An inhibitor of mTOR reduces neoplasia and normalizes p70/S6 kinase activity in Pten$^{+/-}$ mice, PNAS, vol. 98, no. 18, pp. 10320-10325, August 2001.
- YU, mTOR, a novel target in breast cancer: the effect of CCI-779, an mTOR inhibitor, in preclinical models of breast cancer, Endocrine-Related Cancer, vol. 8, pp. 249-258, September 2001.
- DUDKIN, Biochemical correlates of mTOR inhibition by the rapamycin ester CCI-779 and tumor growth inhibition, Clinical Cancer Research, vol. 7, pp. 1758-1764, June 2001.
- International Patent Publication No. WO 00/33878
- Japanese Patent No. JP-A-10-509699 corresponding to International Patent Publication No. WO 96/13273
- Japanese Patent No. JP-A-7-149624 corresponding to US Patent No. 5,516,770
- Japanese Patent No. JP-A-2001-508445 corresponding to International Patent Publication No. WO 98/30205
- Japanese Patent No. JP-A-2001-524988 corresponding to International Patent Publication No. WO 99/45918

The month of publication for documents 5 and 16 could not be determined. The year of publication for this document is sufficiently earlier than the earliest priority date of this application so that the particular month is not in issue (MPEP 609).

Document 5 is a German language document, for which no translation is available. Document 5 was cited in the Wichmann Opposition for interpretation of a portion of German Patent Publication DE 44 18 115A1 (previously cited in an IDS filed November 21, 2003). In interpreting the terms *"1,2-propylene glycol"* and *"lower alcohols such as ethanol"* (see e.g. page 3, lines 60 to 63 of DE 44 18 115A1) and *"polyethylene glycols which have an average molecular weight of 200 to 800"* (see e.g. page 5, lines 47 to 51), the Opponent relied on page 1211, left-hand column, in the upper of the two tables, for an explanation that such polyethylene glycols include polyethylene

glycol 300, polyethylene glycol 400 and polyethylene glycol 600. In addition, document 5 is relied on for disclosing that polyethylene glycol 1000 is a wax in pure form.

The Examiner is respectfully requested to consider the enclosed documents identified in this paper and in the attached document listing during the course of examination of this application.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to our Deposit Account, Number 08-3040.

Respectfully submitted,

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Dated: 9/16/2009

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Appendix 1 to Form 2300 – PRESENTATION OF THE FACTS

Opposition to EP 1 553 940 / 03 771 828.5
Patent proprietor: Wyeth
Opponent: Dr. Hendrik Wichmann

List of contents

GROUNDS

I Prior art / exhibits

The opposition is based on the prior art listed in **Appendix 2**. Documents **D2-D14, D16-D17** and **D19** are prior art pursuant to EPC Article 54(2) since they were all published prior to the priority date of the contested patent. **D15** is a post-published exhibit by way of expert opinion in accordance with the decision **T1110/03** (ABl. 2005, 302, see headnotes II and III). **D18** is prior art pursuant to EPC Article 54(2) for all subject matter for which the filing date of US 60/399,526 (subsequently **D1**) does not apply, such as, for example, the subject matter of claims 16 and 26-30.

II Invalid claiming of the priority (EPC Article 87)

1 Pursuant to EPC Article 87, the right of priority can only be asserted if the European patent application/patent and the application which is intended to substantiate the priority relate to **the same invention**.

2 Upon comparing the relevant information from the supposedly priority-substantiating document **D1** (US patent application No. 60/399,526; see e.g. page 3, line 31 to page 4, line 4) with the technical teaching of the contested patent, the following differences are established:

(i) The subject matter of the contested patent claimed in claims 1, 2 and 22 involves the presence or the use of a *parenterally acceptable solvent*, which also comprises a nonalcoholic solvent (see e.g. claim 2 and section [0016] of the contested patent). By contrast, D1 merely discloses the presence or the use of an *alcoholic solvent* (see e.g. page 3, line 31 to page 4, line 1, page 4, lines 20 to 24, claims 1 and 12, and also Examples 1 and 2 in D1). The use of nonalcoholic solvents is thus not disclosed. Consequently, only the priority of the filing date applies to claims 1, 2 and 22. Since claims 9 to 11 refer back to claims 1 and 2, only the priority of the filing date likewise applies to them.

(ii) On page 3, line 31 to page 4, line 4 in D1, the preferred alcoholic solvent is ethanol, propylene glycol, polyethylene

glycol 300 and polyethylene glycol 400, whereas in the contested patent additionally polyethylene glycol 600 and polyethylene glycol 1000 are specified. These additional features specified in claims 4, 13, 15, 23 and 25 of the contested patent are not mentioned anywhere in the priority-substantiating application. Consequently, only the priority of the filing date applies to these claims.

(iii) On page 3, lines 20 to 23 in D1, the antioxidant (component) is disclosed by way of example as citric acid, D,L-alpha-tocopherol, BHA, BHT, monothioglycerol, ascorbic acid and propyl gallate, whereas the contested patent additionally explicitly mentions glycine. This additional feature specified in claims 5 and 14 of the contested patent is likewise not mentioned in the priority-substantiating application, meaning that the priority of the filing date applies to it.

(iv) According to D1, page 4, lines 24 to 26, the concentration of CCI-779 in the cosolvent concentrate is up to about 50 mg/ml, whereas in the contested patent the concentration of CCI-779 is limited to minimum concentrations of 0.05 mg/ml, 2.5 mg/ml, 5 mg/ml, 10 mg/ml, or of 25 mg/ml up to about 50 mg/ml (see e.g. page 4, lines 8 to 10 of the contested patent). Consequently, in particular the subject matter of claim 9 of the contested patent cannot be directly and clearly inferred from the priority-substantiating application. The priority of the filing date thus applies to claim 9.

(v) The parenterally acceptable, surface-active substance is disclosed in D1 on page 4, lines 6 to 13 in the form of polysorbate 80, a bile acid, lecithin, an ethoxylated vegetable oil, vitamin E tocopherol propylene glycol succinate and a polyoxyethylene/polyoxypropylene block copolymer, whereas the contested patent additionally specifies polysorbate 20 in claims 16 and 26 to 30. This feature cannot be clearly derived from the priority-substantiating application either. Claims 16 and 26 to 30 are therefore not entitled to claim the priority of the priority application.

(vi) The same applies, *mutatis mutandis*, for the concentration range of CCI-779 in the parenteral formulation. Here too, the concentration ranges specified on page 4, lines 10 to 12 and in claim 17 cannot be derived directly and clearly from the priority-substantiating application, which merely discloses a concentration of up to about 25 mg/ml (see page 4, lines 26-29). Examples 3 and 4 of D1 likewise do not disclose a concentration of CCI-779 of 1 mg/ml. Consequently, only the priority of the filing date also applies to claim 17.

(vii) Claim 19 of the contested patent requires a concentration of the antioxidant of 0.0005 to 0.5% w/v of the formulation. This concentration range cannot be directly and clearly inferred from D1 (see e.g. page 3, lines 22 to 23, and also Examples 1 and 2). Consequently, the claiming of the priority is likewise invalid for claim 19.

(viii) The concentration range specified in claim 20 of about 0.5% w/v up to about 10% w/v is not mentioned in the priority-substantiating document D1 (see e.g. page 4, lines 17 to 18, and Examples 3 and 4 in D1). Consequently, only the priority of the filing date also applies to claim 20.

(ix) An indication of the content of solvent, as required in claim 21 of the contested patent, can also not be clearly and directly inferred from the priority-substantiating application. Claim 21 is therefore not entitled to claim the priority.

3 In summary, it remains to be noted that only the filing date applies as an effective date to the subject matter of claims 1, 2, 4, 5, 9-11, 13-17, 19-23 and 25-30. **D18** (interim literature) is thus prior art for these claims pursuant to EPC Article 54(2).

III Lack of novelty (EPC Article 54)

1 Lack of novelty over D2

1.1 **Lack of novelty of claim 1**

1.1.1 Claim 1 is directed to a product and relates to a cosolvent concentrate. The subject matter of the claim is characterized by the following features:

1(A) CCI-779 cosolvent concentrate,

1(B) which comprises CCI-779,

1(C) a parenterally acceptable solvent

1(D) and an antioxidant component.

By virtue of using the term "comprises", this is not an exhaustive list of possible constituents of such a cosolvent concentrate.

1.1.2 **D2** (WO 01/97809) comes under the field of the treatment of cardiovascular, as well as cerebral and peripheral vascular diseases. In particular, D2 discloses various formulations of rapamycin and derivatives thereof.

1.1.3 Claim 31 in conjunction with one of claims 25 to 27 of D2 discloses a product comprising a rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-propionic acid (CCI-779) and an antioxidant as a combined preparation. The features 1(B) and 1(D) are thus satisfied.

1.1.4 D2 further discloses that the carrier may be a solvent, in particular ethanol, a polyol, e.g. propylene glycol or liquid polyethylene glycol, and suitable mixtures thereof (see e.g. page 11, lines 20 to 24, and page 11, line 33 to page 12, line 3). Feature 1(C) is thus likewise satisfied.

1.1.5 According to Part C, Chapter III, Point 4.13 of the examination guidelines of the EPO, feature 1(A) *per se* is not limiting. Rather, this feature only requires that a product must be present in a form which is suitable to be used as cosolvent concentrate. Although, when taken by itself, this feature should already be satisfied, D2 points exclusively to this possibility. Thus, reference is made to parenteral formulations which are preferred and thus specifically individualized within the framework conditions of D2, as are disclosed in the US patents No. 5,530,006 (subsequently **D3**), 5,516,770 (subsequently **D4**),

and 5,616,588 (subsequently **D5**):

> "*Preferred parenteral formulations for administering a rapamycin are disclosed in US Patents 5,530,006; 5,516,770; and 5,616,588, which are hereby incorporated by reference.*"

(see **D2**, page 12, lines 3 to 5; emphasis added)

1.1.6 If a prior publication (the "main document"), here D2, contains an express reference to another prior publication, here D3, D4 and D5, this has the result that when interpreting the main document, the disclosure of the other prior publication(s) must be regarded as part of the disclosure of the main document. **T 0153/85** states in this regard in headnote 4:

> *"The disclosure of a prior publication may on its proper interpretation (i.e. when its meaning to the skilled man is determined) incorporate part or all of another prior publication by specific reference."*

In particular **D3** and **D4** refer in claim 1 to a concentrate solution. Consequently, feature 1(A) is also explicitly co-disclosed by reference to D3 and D4.

1.1.7 All of the features of claim 1 of the contested patent are thus satisfied, which therefore lacks novelty over D2.

1.2 Lack of novelty of claim 2

As already established above in point III 1.1.6, for the interpretation of **D2**, it is possible to use the content of another prior publication for interpreting the meaning. D2 refers on page 12, line 4, in particular in the context of the possible solvents, explicitly to the parenteral formulations of **D3**, which discloses dimethylacetamide as parenterally acceptable solvent:

> *"One aspect of this invention is an aqueous-based, injectable rapamycin solution comprising a concentrate solution of rapamycin in N,N-dimethylacetamide (DMA) in combination with a diluent solution comprising a polyoxyethylene sorbitan ester, polyethylene glycol 300 and water."*

(see **D3**, column 2, lines 20 to 24; emphasis added)

The subject matter of claim 2 is thus anticipated by D2.

1.3 Lack of novelty of claims 3 and 4

1.3.1 As already discussed in the preceding point III 1.1.4, the features of claims 3 and 4 are likewise anticipated by **D2**. In addition, it can be established that D2, taking into consideration the fourth headnote of the decision **T 0153/85**, by reference to **D3** and **D4**, discloses polyethylene glycol 200, polyethylene glycol 300 and polyethylene glycol 400.

1.3.2 Thus, one individualized embodiment of the subject matter of the claimed invention in D2 discloses, by reference to **D3**:

> *"An aqueous, injectable rapamycin solution, said injectable solution consisting essentially of rapamycin in 0.1 to 10 weight percent N,N-dimethylacetamide, 0.09 to 7.5 weight percent of one or more polyoxyethylene sorbitan esters, 9 to 60 weight percent of either polyethylene glycol 200 or 300 or both and 30 to 90 volume percent of water, wherein the concentration of rapamycin in the solution ranges from 0.05 mg/ml to 5.0 mg/ml."*
>
> (see D3, claim 10; emphasis added)

1.3.3 One individualized embodiment described in **D4** also discloses:

> *"An aqueous, injectable rapamycin solution, said injectable solution consisting essentially of rapamycin in 5 to 30 volume percent propylene glycol, 0.07 to 9.5 weight percent of one or more polyoxyethylene sorbitan esters, 7 to 57 weight percent of either polyethylene glycol 200, 300 or 400 or a combination thereof, and 21 to 85.4 volume percent of water, wherein the concentration of rapamycin in the injectable solution ranges from 0.025 mg/ml to 3 mg/ml."*
>
> (see D4, claim 18, emphasis added)

1.3.4 In summary, it can be established that the subject matter of claims 3 and 4 is anticipated by D2.

1.4 Lack of novelty of claim 5

1.4.1 D2 further discloses oral formulations in the form of liquids, suspensions, or solutions (see e.g. page 10, lines 24 to 26), which can comprise, as further constituent, also sodium citrate (page 11, line 3) and glycine (page 11, line 4). In the presence of a solvent, on account of the acid-base equilibrium, some of the sodium citrate will always be present in the form of citric acid. According to D2, such formulations can also be administered parenterally:

> *"The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxyl-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils."*
>
> (see D2, page 11, lines 20 to 24; emphasis added)

Claim 5 therefore lacks novelty over D2.

1.5 Lack of novelty of claim 6

1.5.1 Independent claim 6 contains the following features:

6(A) CCI-779 cosolvent concentrate,

6(B) which comprises CCI-779,

6(C) citric acid

6(D) and dehydrated ethanol.

Analogously to claim 1, the cosolvent concentrate can also have further constituents since the list is not exhaustive.

1.5.2 Features 6(A), 6(B) and 6(C) have already been discussed above in points III 1.1.3-1.1.6, and III 1.4.1 and are regarded as anticipated for the reasons specified.

1.5.3 Compared with the claims of the contested patent discussed hitherto, claim 6, which does also relate to a cosolvent concentrate and not to the parenteral formulation itself, differs by virtue of feature 6(D), which requires that the ethanol is dehydrated. In this regard, it is found that this feature is implicitly disclosed in **D2** since in claims 4, 13, 15, 23 and 25 of the contested patent, exclusively the sole term "ethanol" is used. Accordingly, the generic term "ethanol" includes dehydrated as well as nondehydrated ethanol. In the context with rapamycin, its derivatives and properties thereof, the person skilled in the art would, however, clearly understand this as meaning dehydrated ethanol, as is used, for example, in GB 2 327 611 A (subsequently **D7**), US 4,401,653 (subsequently **D8**), or in Podsypanina et al. (2001) (subsequently **D9**). This clear implicit disclosure also follows from the general specialist knowledge that CCI-779 is poorly soluble in water, to which the contested patent also refers on page 2, lines 43 and 44.

1.5.4 Consequently, feature 6(D), as already discussed under point III 1.1.4, is also satisfied.

1.5.5 Consequently, the subject matter of claim 6 is anticipated completely by D2.

1.6 Lack of novelty of claims 9 and 10

1.6.1 Claim 9 requires that the concentration of CCI-779 in the cosolvent concentrate is from about 0.05 mg/ml to about 50 mg/ml, or from about 25 mg/ml.

1.6.2 The concentration ranges required for CCI-779 are likewise anticipated by D2. As already discussed above in point III 1.1.6, D3 and D4 can also be used for interpreting D2.

1.6.3 **D3** discloses in claim 1 a concentration of the rapamycin in the concentration solution of 0.25 mg/ml to 100 mg/ml. Consequently, a large part of the concentration ranges defined in claims 9 and 10 is anticipated.

1.6.4 **D4** discloses in claim 1 a concentration of the rapamycin in the concentrate solution of 0.5 mg/ml to 10 mg/ml, which is clearly within the concentration range claimed in claim 9 of the contested patent.

1.6.5 In view of the above arguments, claims 9 and 10 consequently lack novelty over D2.

1.7 Lack of novelty of claims 12 to 16

1.7.1 Independent claim 12 has the following features:

12(A) parenteral formulation,

12(B) which comprises CCI-779,

12(C) an alcoholic solvent,

12(D) an antioxidant,

12(E) a dilution solvent

12(F) and a surface-active substance.

In this claim too, the list of constituents is not exhaustive on account of the use of the term "comprises".

1.7.2 **D2** also expressly discloses parenteral formulations (see e.g. page 11, lines 20 to 21 and 28 to 30, page 12, lines 3 to 5). Feature 12(A) is thus satisfied.

1.7.3 It has already been shown above that the features 12(B), 12(C), and 12(D) (see III 1.1.3 and III 1.1.4) are likewise satisfied.

1.7.4 The diluent solvent is defined in the contested patent such that it encompasses water, ethanol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600 and polyethylene glycol 1000 (see page 3, line 57 to page 4, line 2 of the contested patent). The diluent solvent thus encompasses all solvents which, in the contested patent, also fall under the definition of an "alcoholic solvent". This feature is thus always satisfied in the

case of the presence of an alcoholic solvent. Additionally, the diluent solvent differs from the alcoholic solvent by the solvent water. However, D2 also discloses water as solvent:

> *"The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils."*
>
> (see D2, page 11, line 33 to page 12, line 3; emphasis added)

Consequently, feature 12(E) is satisfied.

1.7.5 Finally, **D2** also discloses the feature 12(F) directly and clearly, e.g. on page 11, lines 6 to 11 and in particular lines 21 to 23 in D2, where it reads:

> *"The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxyl-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils."*
>
> (see D2, page 11, lines 20 to 24; emphasis added)

1.7.6 A further disclosure consists in turn in the reference to **D3** (see e.g. claims 1, 2 and 10, and also column 3, lines 64 to 66) and in **D4** (see e.g. claims 1, 2 and 18, and also column 4, lines 42 to 44), which both disclose polysorbate, 20, 60 or 80 as surface-active substance.

1.7.7 Feature 12(F) is thus likewise satisfied.

1.7.8 Consequently, all of the features of claim 12 are satisfied, resulting in lack of novelty over D2. The same is true for the subject matters of claims 13 to 16 that depend on claim 12 (see also D2, claim 31 in conjunction with 25-27).

1.8 Lack of novelty of claims 17, 18, 20 and 21

1.8.1 As already mentioned above, the term "about" is not clearly defined and is therefore not limiting. Nevertheless, the Opponent establishes that D2 – analogously to the explanation in point III 1.6 – refers directly and clearly to the formulations of in particular D3 and D4.

1.8.2 These documents disclose, in the respective main claim, a rapamycin concentration of from 0.025 mg/ml to 3 mg/ml (**D4**), or 0.05 mg/ml to 5 mg/ml (**D3**). Consequently, the features of claims 17 and 18 are disclosed.

1.8.3 The subject matter of claims 20 and 21 is anticipated by claim 10 in **D3**, and by claim 18 in **D4** in a manner prejudicial to novelty.

1.8.4 Claims 17, 18, 20 and 21 are consequently not novel over D2.

1.9 Lack of novelty of claims 22 to 26

1.9.1 Claim 22 relates to a process for the preparation of a parenteral CCI-779 formulation and has the following features:

22(A) Process for the preparation of a parenteral CCI-779 formulation, involving:

22(B1) (a) mixing of CCI-779

22(B2) with a parenterally acceptable solvent

22(B3) and an antioxidant component,

22(B4) in order to produce a cosolvent concentrate,

22(C1) (b) mixing a dilution solvent

22(C2) and a surface-active substance

22(C3) in order to prepare a diluent; and

22(D1) (c) mixing the cosolvent concentrate with the diluent

22(D2) in order to produce the parenteral CCI-779 formulation.

Claim 23 defines the solvent in more detail, it remaining open whether this is the parenterally acceptable solvent, the dilution solvent, or both. Claim 24 defines the antioxidant, claim 25 the dilution solvent and claim 26 the surface-active substance.

1.9.2 **D2** discloses the combination of CCI-779 (feature 22(B1)) and an antioxidant component (feature 22(B3), claim 24), as discussed above. In particular parenteral formulations are disclosed by clear and direct reference to D3 and D4:

1.9.3 **D3** discloses in Example 1 the mixing of rapamycin with dimethylacetamide (features 22(B2) and 22(B4)). Example 3 describes a process for the preparation of the diluent (feature 22(C3)) by mixing polyethylene glycol 300, polysorbate 80 (feature 22(C2), claim 26) and water (feature 22(C1), claim 25), and also the mixing of the cosolvent concentrate solution prepared according to Example 1 with the diluent (features 22(D1) and 22(D2)).

1.9.4 **D4** discloses in Example 3 the mixing of rapamycin with polypropylene glycol (features 22(B2) and 22(B4), claim 23), the mixing of a diluent (feature 22(C3)) from polyethylene glycol 400, polysorbate 80 (feature 22(C2), claim 26) and water (feature 22(C1)), and also the mixing of the concentrate solution with the dilution solution (features 22(D1) and 22(D2), claim 25).

1.9.5 For the reasons described above, claims 22 to 26 lack novelty over D2.

1.10 Summary and conclusion

1.10.1 D2 anticipates the subject matter of claims 1-6, 9-10, 12-18 and 20-26 in a manner prejudicial to novelty.

2 Lack of novelty over D7

2.1 Lack of novelty of claims 1 and 3-5 over D7

2.1.1 **D7** (GB 2327611 A) comes under the same technical field as the contested patent since it relates to formulations of rapamycin and derivatives thereof. As

an example of known derivatives of rapamycin, reference is made in particular on page 1, lines 31 and 32 to WO 94/02136 (**D10**). Claim 1 of D10, which includes a generic formula, contains a disclaimer which stipulates that when Y is –R10, R10 is not a methyl radical, as a result of which CCI-779 is explicitly omitted. According to Part C, Chapter III, Point 4.20 of the examination guidelines of the EPO, such disclaimers are inserted in order to exclude nonpatentable (novelty-destroying) embodiments which would nevertheless work. It was therefore clear to the person skilled in the art that in particular the invention with CCI-779 claimed in D10, and thus also in D7 exists. Consequently, CCI-779 is implicitly disclosed by reference to D10.

2.1.2 Examples 2 and 3 on pages 5 and 6 of **D7** disclose a cosolvent concentrate ("preconcentrates", page 5, line 31) using ethanol, propylene glycol and D,L-alpha-tocopherol.

2.1.3 Claims 1 and 3-5 are therefore not novel over D7.

2.2 Lack of novelty of claim 6

2.2.1 Example 5 in **D7** discloses a concentrate using citric acid and ethanol. Examples 2 and 3 in D7 disclose a concentrate which comprises absolute ethanol and malonic acid. According to page 4, lines 19 to 22, the malonic acid can also be replaced by citric acid.

2.2.2 Claim 6 is therefore not novel over D7.

2.3 Lack of novelty of claims 7-11

2.3.1 Examples 2 and 3 disclose concentrate solutions which comprise absolute (dehydrated) ethanol, D,L-alpha-tocopherol and propylene glycol.

2.3.2 As already explained in point III 2.2.1, D7 teaches that the malonic acid used can be replaced by citric acid. The concentrate solution then comprises both D,L-alpha-tocopherol, and also citric acid.

2.3.3 According to **D7**, the rapamycin derivative, which also includes CCI-779 (see above point III 2.1.1), is present in the formulation in an amount of 2%, which corresponds to a concentration of 20 mg/ml. In Example 5 of D7, a

concentration of the rapamycin derivative of 20 mg/ml is likewise used. This concentration lies within the concentration range required in claim 9, and also at about 25 mg/ml.

2.3.4 Example 2a in **D7** additionally discloses an antioxidant concentration of 0.1% and therefore anticipates the subject matter of claim 11 in a manner prejudicial to novelty.

2.3.5 Claims 7-11 thus lack novelty over D7.

2.4 Lack of novelty of claims 12-17, 19 and 21

2.4.1 According to **D7**, the acid-stabilized compositions can also be administered parenterally, e.g. as an infusion concentrate (see e.g. page 5, lines 4 and 5). This includes compositions which comprise CCI-779 (see point III 2.1.1). The features of claim 12 are thus satisfied.

2.4.2 As already discussed above, Examples 2 and 3 of **D7** disclose solutions which comprise absolute ethanol, propylene glycol and D,L-alpha-tocopherol. Since the alcoholic solvent and the dilution solvent may each both be ethanol or propylene glycol, the ethanol here is either the alcoholic solvent and propylene glycol is the dilution solvent, or the propylene glycol is the alcoholic solvent and the ethanol is the dilution solvent. Alternatively, the ethanol or the propylene glycol can also be the alcoholic solvent and the dilution solvent at the same time. Taken together or alone, the ethanol and the propylene glycol constitute about 10% to about 90% of the formulation.

2.4.3 Additionally, the solutions of Examples 2 and 3 also comprise the surface-active substance Cremophor RH40. Cremophor is a trade name of an ethoxylated vegetable oil.

2.4.4 In the examples listed, the active agent (CCI-779) is present in a concentration of 20 mg/ml.

2.4.5 The weight fraction of the antioxidant D,L-alpha-tocopherol in the formulation of Examples 2 and 3 in D7 is 0.1% and is thus within the range from 0.0005% to 0.5% (w/v) required in claim 19.

2.4.6 All of the features of claims 12-17, 19 and 21 are thus satisfied. Consequently, these claims lack novelty over D7.

2.5 Summary and conclusion

2.5.1 D7 anticipates the subject matter of claims 1, 3-17 and 19 and 21 in a manner prejudicial to novelty.

IV Lack of inventive step (EPC Article 56)

1 Field of the contested patent and general expert knowledge

1.1 The contested patent relates in general to the field of the parenteral formulation of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methyl-propionic acid (CCI-779). According to the contested patent, the object is to provide a parenteral formulation which (a) increases the solubility of CCI-779 by using water-miscible organic solvents, (b) reducing the oxidative degradation in order to thereby increase the *chemical* stability, and (c) permits the dilution of an organic solution of CCI-779 with an aqueous solution without precipitation of the active ingredient, i.e. increases the *physical* stability of the formulation (see e.g. section [0009] of the contested patent.

1.2 Even in March 1996, i.e. several years prior to the priority date, Sweetana and Akers (**D11**) discussed in a review article the known principles and possibilities of formulating sparingly water-soluble or water-insoluble active ingredients for parenteral administration. Since CCI-779, as the contested patent fittingly establishes on page 2, lines 44 and 45, is not an electrolyte and a pH change for the formulation of an ester is not expedient, according to D11, the use of water-miscible cosolvents, surface-active substances and complexing agents is the most obvious approach for the person skilled in the art:

> *"Often a useful approach to increase the aqueous solubility of an ionizable drug is pH adjustment. The next approach most frequently tried is the use of water-miscible cosolvents. Other approaches to be discussed briefly include the use of surface active agents and complexing agents."*

(see e.g. D11, page 331, right-hand column, lines 9 to 14; emphasis added)

In Table I on page 331, D11 discloses examples of suitable cosolvents, such as polyethylene glycol, propylene glycol and dimethylacetamide, examples of surface-active substances, such as polysorbates, poloxamers (a trivial name for polyoxyethylene-polyoxypropylene block copolymers), Cremophor EL (a trade name for an ethoxylated vegetable oil), lecithin and bile acids, and also complexing agents, such as soluble vitamins. Suitable concentrations of cosolvents and surface-active substances are shown below on page 334 in Table III, and on page 335 in Table IV of D11.

The role of the surface-active substances is discussed in detail on page 336, left-hand column, under point C. Besides further examples of suitable surface-active substances, their function is also discussed:

"Surface active agents are usually incorporated into parenterals to provide one of several desirable properties; 1) increase drug solubility through micellization, 2) prevent drug precipitation upon dilution, 3) improve the stability of the drug in solution by incorporation of the drug into a micellar structure, [...]"

(see D11, page 336, left-hand column, first paragraph under point C; emphasis added)

D11 thus taught how the problems addressed in the contested patent can be solved by adding a surface-active substance.

1.3 Strickley et al. (1999) **(D12)** is a further review article on parenteral formulations which documents the general expert knowledge. In agreement with Sweetana and Akers, D12 establishes:

"If the drug molecule is not ionizable then pH has no effect on solubility, but solubility enhancement can often be accomplished by a combination of aqueous and organic solvents (i.e. a cosolvent). The currently used organic solvents used in mixed organic/aqueous formulations are propylene glycol, ethanol, polyethylene glycol 300 or 400, Cremophor EL, Tween 80, sorbitol, glycerin and dimethylacetamide (DMA) (Table

VI). [...] Many cosolvent formulations are marketed using rather high concentrations of organic solvent, and are usually but not always diluted prior to injection."

(see page 328, right-hand column, penultimate line to page 329, left-hand column, line 12; emphasis added).

Furthermore, D12 explicitly discloses for tacrolimus (a lactam macrolide, structurally similar to the rapamycin class) a formulation in which rapamycin is present in a concentrate consisting of 80% ethanol and 20% Cremophor EL which can furthermore be diluted 250-1000 times into an aqueous vehicle (see page 333).

Consequently, the combination of a cosolvent, a surface-active substance and an aqueous dilution solution was already known and general expert knowledge! The process for preparing such parenteral formulations through dilution and other (alcoholic) solvents suitable for such parenteral formulations were also already well known to the person skilled in the art.

1.4 Powell et al. (1998) (**D13**) is a further review article documenting the expert knowledge which deals with auxiliaries for parenteral formulations. As early as in the second and third sentence of this article, the authors establish:

"It is rational in the sense that certain types of excipients are added to alter the formulation properties: i) buffers of appropriate pKa are added to control hydrogen ion concentration at a desired pH, ii) tonicifiers are added for biocompatibility, iii) surfactants are added when necessary to prevent aggregation, adsorption to surfaces, or increase solubility, iv) antioxidants are included to prevent unwanted oxidation of the drug, and so on. The inclusion of various classes of formulation components, and the concentration used is often quite rational, in that their behavior and properties are known, and they are added to prevent specific problems that would arise in their absence."

(see page 238, left-hand column, lines 2 to 14; emphasis added)

In one list, Powell et al. then detail constituents of already known parenteral formulations, including a large number of the cosolvents, surface-active

substances and antioxidants already specified in D11 and D12, such as, for example, citric acid.

1.5 Sorbera et al. (January 2002) (**D14**) is likewise a review article documenting the expert knowledge which deals with the advantageous pharmacological properties of CCI-779. Page 10, left-hand column, second paragraph states:

> *"Although rapamycin has shown excellent preclinical anticancer activity, its clinical development has been hampered due to the poor aqueous solubility and chemical stability of the macrolide. The response has been development of soluble C-42 hydroxyester and amidino carbamate analogs. CCI-779, a rapamycin ester derived from 2,2-bis(hydroxymethyl)propionic acid, is one such analog that was selected for further development as an i.v. anticancer agent due to its promising pharmacological, toxicological and antitumor profiles."*
>
> (emphasis added)

The particular importance of CCI-779 is demonstrated in D14 later on on page 11 by the detailed clinical studies. In the right-hand column, last paragraph, even a phase II study, and also a planned phase III study are mentioned. Among the numerous rapamycin derivatives, CCI-779 was the most promising for the person skilled in the art, and its pharmacological advantages over rapamycin and its derivatives clearly belonged to the general expert knowledge.

1.6 In summary, it can be established that on the priority date of the contested patent the use of cosolvents for increasing the solubility in water was well known. It was general expert knowledge that surface-active substances are suitable for increasing the solubility and the physical stability, in particular in the case of the dilution of sparingly water-soluble active ingredients in aqueous solutions. Furthermore, even years prior to the priority date it belonged to the routine measures for protecting an active ingredient against oxidative degradation by adding antioxidants. At this time, it was also common practice to formulate sparingly water-soluble active ingredients in cosolvent concentrates which are then diluted prior to administration. CCI-779 was known as the most pharmacologically promising derivative of rapamycin.

In view of this, the aim of the next section is to critically assess the supposed contribution of the contested patent to the prior art.

2 **Lack of inventive step - failure to solve the problem over the entire range of the claims**

2.1 The granted claims lack an inventive step since the contested patent makes no contribution to the prior art over the entire claimed range of the claims, as is required by established EPO case law.

2.2 Claims 1 to 21 relate to a CCI-779 cosolvent concentrate or a parenteral CCI-779 formulation comprising CCI-779, a parenterally acceptable solvent and an antioxidant, including citric acid and ascorbic acid, in particular in a concentration of about 0.001% to 1.0% w/v, or 0.0005% to 0.5% w/v. However, the description in the contested patent in no way shows the desired technical effect for essentially all of the claimed embodiments.

2.3 Examples 1 to 3 show supposedly stabilized cosolvent concentrates. In all three examples, the fraction of citric acid is at most 0.005% w/v. This especially is of great importance because the content of the antioxidant can on the one hand be up to 1% w/v (see claim 11), although on the other hand it is stated:

> *"In one example, citric acid enhanced the stability of CCI-779 when used at a concentration of less than 0.01% w/v. Higher concentrations are less stable solutions and thus, less desirable for products to be subject to long-term storage in liquid form."*
>
> (see page 3, lines 42 to 44 of the contested patent, and also page 3, lines 23 to 25 of the priority-substantiating document **D1**; emphasis added)

This arises in particular also from the package leaflet for the product based on the contested patent which originates from the patent proprietor himself (**D15**). In this, the patent proprietor himself declares:

> *"Temsirolimus is degraded by both acids and bases, and thus combinations of temsirolimus with agents capable of modifying solution*

pH should be avoided."

(see D15, page 4, first full paragraph, last sentence; emphasis added)

Nevertheless, the contested patent teaches:

"Acceptable antioxidants include, but are not limited to, citric acid, d,l-alpha-tocopherol, BHA, BHT, monothioglycerol, ascorbic acid, propyl gallate, and mixtures thereof. Generally the formulations of the invention will contain an antioxidant component in a concentration ranging from 0.001% to 1% w/v, or 0.01% to 0.5% w/v, of the cosolvent concentrate, although lower or higher concentrations may be desired. [...] In certain embodiments, the antioxidant component of the formulation of the invention also exhibits chelating activity. Examples of such chelating agents include, e.g. citric acid, acetic acid, and ascorbic acid [...]."

(Page 3, lines 29 to 37; emphasis added)

Furthermore, each of Examples 1 to 3 includes citric acid, which is known to stabilize rapamycin in small amounts (see e.g. **D7**), although not a single example is shown in which D,L-alpha-tocopherol is used as the sole antioxidant. It is therefore completely unclear whether D,L-alpha-tocopherol in combination with citric acid has a synergistically stabilizing effect.

Independently of this, it should be emphasized that none of the examples exhibits any kind of direct proof of an advantageous technical effect. In none of the examples was a comparison sample without antioxidant carried out. Instead, imprecise statements were made, such as "shelf-life of 18-30 months" (see Example 1), "good stability", or "no significant degradation" (in each case Example 2). Further data which backs up these statements is not given. What is good or significant is not defined and is at the discretion of the reader. Consequently, Examples 1 to 3 do not constitute a contribution to the prior art which would justify protection in terms of patent rights.

2.4 Example 4 was already published prior to the priority date apart from the use of an antioxidant in the cosolvent concentrate according to Example 1 in the present form. In Podsypanina et al., 2001 (**D9**), on page 10320, right-hand

column, last full paragraph, CCI-779 is firstly dissolved in absolute ethanol (cf. Example 1 of the contested patent), and then diluted with a vehicle which comprises 5% Tween 80 (trade name for polysorbate 80) and 5% polyethylene glycol 400. It is naturally clear to the person skilled in the art that when the cosolvent concentrate is prepared a relatively long time before its use, its chemical stability can be increased by an antioxidant (see e.g. **D13**) in order to reduce oxidative degradation. Example 4 thus does not constitute a new contribution to the prior art.

2.5 Examples 5, 6, 7 and 9 each disclose parenteral CCI-779 formulations obtained through different dilution solutions which are physically stable for several hours at room temperature. Thus, no statement is made about the chemical stability. It is also not defined what is meant by several hours, nor are other further data shown in order to support this claim. Example 5 is even purely hypothetical (*"could be suitable for direct intravenous injection"*; emphasis added).

Furthermore, prior to the time of the priority date, it was general expert knowledge that surface-active substances can increase the physical stability (see e.g. **D11**). Examples 5, 6, 7 and 9 thus constitute obvious alternatives, in particular in relation to an example which is already described in **D11** on page 335 in Table IV, last line (10% polysorbate 80). They are therefore not a new contribution to the prior art.

2.6 Examples 4 and 8 are both supposedly intended to provide a chemically and physically stable parenteral formulation. Both examples have failed insofar as they do not show any kind of comparison data or other data as proof of this claim. Furthermore, both examples teach that the parenteral formulation *can* be diluted either with a 0.9% sodium chloride solution or a 5% dextrose solution. **D15** teaches, on the other hand:

> *"It is recommended that TORISEL be administered in 0.9% sodium chloride injection after combining with diluent. The stability of TORISEL in other infusion solutions has not been evaluated."*
>
> (see D15, page 4, lines 4 to 6 of the first full paragraph, emphasis added)

This is a clear indication that a dilution of the parenteral formulations, contrary to the claim in Examples 4 and 8, was actually never tested in a 5% dextrose solution.

Finally, it remains to be noted that Examples 4 and 8 were used exclusively in combination with the cosolvent concentrates from Examples 1 and 2, although claim 22 is directed to parenterally acceptable solvents, which also includes cosolvent concentrates which use dimethylacetamide. Since both examples do not demonstrate the claimed technical effect through data, both examples do not constitute a new contribution to the prior art.

It is further pointed out that Example 8, after mixing with the cosolvent concentrate (1.5:1), has a content of surface-active agent which does not satisfy the requirement of claim 20 that the surface-active substance constitutes 0.5% to 10% w/v of the formulation.

2.7 In conclusion it is stressed that the contested patent essentially provides no new experimental data, let alone data which demonstrates a surprising technical effect with regard to increased solubility, as well as an increased chemical and physical stability for the specific compositions of the examples over the compositions of the prior art (see e.g. the teachings of **D11** and **D8** (see also below under point IV 3.7)).

The examples show no data which could justify a concentration range > 0.1% w/v of the antioxidant, let alone any unexpected technical effect of a combination of D,L-alpha-tocopherol and citric acid. On the contrary, the contested patent teaches nonfunctioning embodiments.

Even the dilution solution described in Example 8, which the patent proprietor ultimately intends to market industrially (see **D15**, page 13, second paragraph), was not present in this form at the time of the priority date since there, in Example 4 of the priority application corresponding to this, the content of polysorbate was 33.3% w/v. Contrary to the contested patent, furthermore, **D15** teaches that a use of 5% dextrose solution should be avoided as infusion solution. These facts ultimately only lead to the conclusion that at the time of filing the priority application, the applicant had not even made the claimed invention.

2.8 In summary, on account of the lack of any data, the contested patent can in no way explain that every antioxidant, even in the concentration ranges mentioned in the description, which are not even a constituent of the independent claims, has the desired technical effect of stabilizing CCI-779.

2.9 Consequently, a large part of the embodiments which fall within the scope of the current claims, does not solve the problem addressed although the patent proprietor was responsible for showing that it is achieved over the entire range of the claims before submitting the application (see e.g. **T 0583/93**, point 7.5 of the reasoning; **T 1329/04**).

2.10 Furthermore, the technical effect on which the Examination Division has possibly substantiated the presence of an inventive step is not present over the entire range of the claims. For this reason, there is an unacceptable imbalance between the scope of the claims and the supposed contribution to the prior art (**T 0939/92; T 0338/04**, point 15 of the reasoning).

2.11 Consequently, the claims of the contested patent do not meet the requirement of EPC Article 56.

3 Lack of inventive step in relation to the closest prior art

In the unlikely event of the Opposition Division coming to a different conclusion, the claimed subject matter must inevitably be regarded as obvious in the light of the relevant prior art.

3.1 Claims 1 to 11 lack an inventive step compared with D16 alone or in combination with D17

3.1.1 **D16** (DE 44 18 115 A1) could be regarded as the closest prior art. The document relates to the technical field of the galenic formulation of compounds of the rapamycin class (page 2, lines 1 to 2), which includes rapamycin and its structurally similar analogues and derivatives (see e.g. page 2, lines 44 to 45), which includes CCI-779, although it does not mention it by name. Although D16 relates in particular to formulations for oral administration, it has the same object as the contested patent, namely to provide a formulation which has improved solubility and improved stability of the active ingredient (see e.g. D16, page 2, lines 47 to 48 in combination with

lines 61 to 63). Since the formulations described in D16 are likewise liquid, indeed even have the same parenterally acceptable solvent, the person skilled in the art would have considered D16 to be a promising springboard for preparing a parenteral formulation through minimal, obvious modifications which falls under the wording of the claims.

3.1.2 In detail, **D16** discloses *"emulsion preconcentrates"*, which also include *"antioxidants (such as ascorbyl palmitate, butylhydroxyanisole (BHA), butylhydroxytoluene (BHT) and tocopherols)"*, which can *"comprise approximately 0.05 to 1% by weight of the total weight of the composition"* (page 6, lines 56 to 62). Here, the antioxidant is *"preferably alpha-tocopherol"* (page 6, line 64). The formulations of D16 also comprise parenterally acceptable solvents, such as, for example, *"1,2-propylene glycol"* and *"lower alcohols such as ethanol"* (see e.g. page 3, lines 60 to 63) and *"polyethylene glycols which have an average molecular weight of 200 to 800"* (see e.g. page 5, lines 47 to 51). For interpretation, the Opponent refers to an extract, available to the person skilled in the art at the time of the filing date of the priority application, from a reference work by Fiedler, "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete [Lexikon of auxiliaries for pharmacy, cosmetics and related fields]" (1996) (**D6**), where it can be found, on page 1211, left-hand column, in the upper of the two tables, that such polyethylene glycols include polyethylene glycol 300, polyethylene glycol 400 and polyethylene glycol 600. According to Example 3 in **D16**, which exhibits such a (micro)emulsion preconcentrate (see page 9, line 50), the fraction of rapamycin in such a (micro)emulsion preconcentrate is 2% and is thus within the required concentration ranges of the contested patent.

3.1.3 The contested patent thus differs from **D16** merely in that it expressly mentions CCI-779. The problem addressed could be considered that of providing a formulation with another rapamycin derivative which avoids the known disadvantages of rapamycin. This problem is (supposedly, see above) solved by the CCI-779-containing formulation according to claim 1.

3.1.4 The advantages of CCI-779 over other rapamycin derivatives are clearly known for the person skilled in the art from **D17** (Garber, 2001). On page 4, second full paragraph, D17 establishes:

"Wyeth-Ayerst synthesizedand [sic] tested hundreds of rapamycin

analogues, both to stay ahead of competitors and to extend patent life. The best one was CCI-779."

(emphasis added)

In the last paragraph of D17, the following conclusion is drawn:

"CCI-779's uniqueness is its biggest advantage."

(emphasis added)

There is no doubt in the slightest that it was obvious to a person skilled in the art, in the knowledge of D17, at the time of filing the priority application to select precisely CCI-779 from the large number of rapamycin derivatives.

3.1.5 Since the choice of CCI-779 was obvious as the known rapamycin derivative to the person skilled in the art in the light of **D17** or even general expert knowledge (see **D14**; see above under point IV 1.5), the subject matter of claims 1, 3-5, 7 and 9-11 lacks any inventive step starting from D16 in the light of the general expert knowledge or in combination with D17.

3.1.6 The subject matter of claims 2, 6 and 8 relates to obvious variants of the formulations described in D16, which are unable to substantiate an inventive step.

3.2 Claims 12 to 21 lack an inventive step compared with D16

3.2.1 The microemulsion preconcentrate of **D16** is described as spontaneously forming a microemulsion in an aqueous composition (see e.g. page 3, lines 16 to 17). Moreover, the described microemulsion preconcentrates can comprise suitable surface-active substances. These are described in great detail in D16 on page 5, line 64 to page 6, line 43 and include Cremophor, polysorbates, poloxamers and lecithins. In Example 3, these are present in a concentration of 41.5%; however, it will have been obvious to a person skilled in the art that following dilution with for example water, the final content of surface-active substance and of dilution solvent lies within the limits required in claims 20 and 21. The same applies analogously for the concentration of the active ingredient and the concentration ranges required in claims 17 and

18 of the contested patent.

3.2.2 Analogously to the conclusions in IV 3.1.3 to 3.1.5, corresponding considerations therefore apply for claims 12 to 21. Claims 12 to 21 therefore lack an inventive step compared to D16 in view of the general expert knowledge or in combination with D17.

3.3 Claims 22 to 30 lack an inventive step compared to D16

3.3.1 As already mentioned above, **D16** describes the preparation of a formulation, suitable for parenteral administration, of rapamycin derivatives by diluting the emulsion preconcentrate with water:

> *"A "microemulsion preconcentrate" is defined in this description as a formulation which spontaneously forms a microemulsion in an aqueous composition, for example water or in the gastric juices following oral administration."*
>
> (see D16, page 3, lines 16 to 18; emphasis added)

The process according to claim 22, however, requires that the dilution solvent must comprise the surface-active substance. D16 also, however, gives an indication of this:

> *"In addition, the pharmaceutical composition is effective with surfactant materials, for example bile salts, which are present in the gastrointestinal tract. This means the pharmaceutical composition can be completely dissolved in aqueous systems which comprise such natural surfactants, and can therefore deliver microemulsion systems in situ which are stable and does not exhibit precipitation of the active constituent or other disturbances of the fine particle structure."*
>
> (see D16, page 7, lines 20 to 24; emphasis added)

D16 thus teaches that the surface-active substance may also be present in the aqueous diluent and this leads to a stabilization, in particular a physical stabilization.

3.3.2 Analogously to the conclusions in IV 3.1.3 to IV 3.1.5, corresponding considerations therefore apply for claims 12 to 21.

In addition, it would be obvious to a person skilled in the art to replace bile salts with other surface-active substances because bile salts were known in the general expert knowledge in connection with surface-active substances (see e.g. Sweetana and Akers, **D11**). All of the further particular embodiments are, as already explained above, obvious variants and are unable to substantiate an inventive step. Claims 22 to 30 are consequently not novel compared with D16.

3.4 Claims 1 to 11 lack an inventive step compared with D9 or D18 alone or in combination with D19

3.4.1 Podsypanina et al., 2001 (**D9**) is a scientific article on a functional study which involves the parenteral administration of CCI-779. D9 discloses a parenteral CCI-779 formulation which was prepared by diluting a 50 mg/ml CCI-779 stock solution in absolute ethanol with a dilution solution which comprises 5% Tween-80 and 5% polyethylene glycol-400 in a parenterally acceptable solvent (see page 10320, right-hand column, last complete paragraph).

3.4.2 Grünwald et al., published on 28 August 2002 (**D18**), likewise describes a functional study in which CCI-779 is administered parenterally. The document discloses a parenteral CCI-779 formulation which was prepared by diluting a 50 mg/ml CCI-779 stock solution in absolute ethanol with a dilution solution which comprises 5% Tween-20 and 5% polyethylene glycol-400 in an aqueous 0.15 M NaCl solution (see page 6142, left-hand column, last complete paragraph). As explained above under point II (iv), only the filing date of the patent application of the contested patent applies as priority to all of the claims which mention polysorbate 20 as possible surface-active substance. **D18** is consequently prior art pursuant to EPC Article 54(2).

3.4.3 Compared to the contested patent, the cosolvent concentrates of **D9** or **D18** do not comprise an antioxidant. The problem addressed thus consists in preparing a more chemically stable cosolvent concentrate of CCI-779. The cosolvent concentrates of claims 1, 6 and 7 which comprise an antioxidant were reportedly the (alleged, see above) solution.

3.4.4 WO 00/33878 (**D19**) already describes the stabilization of rapamycins and rapamycin derivatives against oxidative degradation through antioxidants (see page 1, first and second paragraph). As suitable concentration, D19 teaches on page 1 under point 1, second paragraph:

> *"The amount of antioxidant may conveniently be up to 1%, more preferably from 0.01 to 0.5% (based on the weight of the macrolide). Such small amount is referred hereinafter as a catalytic amount."*
> (emphasis added)

Further disclosure in D19 for an antioxidant concentration which falls under the wording of the claims of the contested patent can also be found on page 3, third paragraph, and also in claims 1 to 3.

Furthermore, D19 mentions in the second paragraph on page 3 preferred antioxidants, namely BHT, vitamin E (tocopherol) and vitamin C (ascorbic acid), as are specified in claims 5 and 16.

3.4.5 In **D9** and in **D18**, the cosolvent concentrate is freshly prepared. In the light of the general expert knowledge, it was obvious to the person skilled in the art that if a cosolvent concentrate were to be prepared a relatively long time before the dilution, it would be chemically stabilized using preservatives. This alone would lead the person skilled in the art to the claimed solution of adding an antioxidant (if desired also a chelating agent, such as citric acid or ascorbic acid, which, however, are also simultaneously antioxidants). In the search for an antioxidant which is particularly suitable for CCI-779, the person skilled in the art would invariably encounter the teaching of **D19** and take this into consideration.

3.4.6 Consequently, the subject matter of claims 1, 3-7, 9 and 11 is obvious to a person skilled in the art in the knowledge of D9 and/or D18 in the light of the general expert knowledge or in view of D19.

3.4.7 In the light of the general expert knowledge, the subject matter of claims 2, 8 and 10 relates to trivial embodiments which do not substantiate an inventive step.

3.4.8 Consequently, claims 1 to 11 lack an inventive step.

3.5 Claims 12 to 21 lack an inventive step compared with D9 or D18 alone or in combination with D19

3.5.1 The end concentration of CCI-779 in the parenteral formulations of **D9** and/or **D18** is 2 mg/ml. D18 additionally specifies the dilution solvent as water.

3.5.2 The conclusions in IV 3.4.3 to 3.4.5 therefore apply accordingly for claims 12 to 21.

The subject matter of claims 12-17 and 19-21 is obvious to a person skilled in the art in the knowledge of the teaching of D9 and/or D18 in the light of the general expert knowledge or in view of D19.

Furthermore, the subject matter of claim 18 is not inventive on the one hand through the use of the term "about 2.5 mg/ml", which can include a concentration of 2 mg/ml, or in the sense of an obvious variant.

Consequently, claims 12 to 21 lack an inventive step.

3.6 Claims 22 to 30 lack an inventive step compared with D9 or D18 alone or in combination with D19

3.6.1 The conclusions in IV 3.4.3 to 3.4.5 therefore apply accordingly for claims 22 to 30.

3.6.2 The subject matter of claims 22-26 is obvious to the person skilled in the art in the knowledge of the teaching of **D9** and/or **D18** in the light of the general expert knowledge or in view of D19. With the general expert knowledge at the time of the filing date, the subject matter of claims 27 to 30 is in each case an obvious variant which does not exhibit a surprising technical effect. Claims 22 to 30 also lack an inventive step.

3.7 Claims 1 to 21 lack an inventive step compared with D8

3.7.1 **D8** (US 4,401,653) relates to a combination therapy using rapamycin and a further active ingredient. Example 1 describes an injectable rapamycin preparation with the following composition: 5.5 mg/ml rapamycin, 0.1 mg/ml

BHA (corresponds to 0.01% w/v), 75 mg (7.5% w/v) absolute ethanol, 100 mg (10% w/v) Cremophor EL and 1 ml (q.s.) water.

3.7.2 The cosolvent concentrate claimed in the contested patent and the claimed parenteral formulation of the contested patent differ only through the presence of a surface-active substance and of a dilution solvent. Since the features of claims 1, 6 and 7 are not exhaustive (*"comprises"*), and the concentration range of CCI-779 required in claim 9 is greater than that in claims 17 and 18, simultaneously each parenteral formulation of the contested patent is at the same time a cosolvent concentrate of the contested patent.

3.7.3 **D8** and the contested patent differ exclusively in the point that D8 relates to rapamycin and not to the rapamycin derivative CCI-779. The problem addressed could be considered that of providing a parenteral formulation (a cosolvent concentrate) which comprises a rapamycin derivative with improved pharmacological properties. The solution consists (supposedly, see above) in a formulation or a cosolvent concentrate according to claims 1, 6, 7 and 12 of the contested patent.

3.7.4 On the basis of the general expert knowledge, the pharmacological advantages of CCI-779 over rapamycin, in particular the better solubility and increased chemical stability, were well known to the person skilled in the art (see e.g. **D14**). It was therefore absolutely obvious to the person skilled in the art to use the rapamycin derivative CCI-779 in exchange for rapamycin. Logically, the subject matter of claims 1 to 21 cannot be inventive.

3.8 Claims 1-30 lack an inventive step compared with D2

3.8.1 Only for the sake of completeness is it noted that in the unlikely event that the Opposition Division should come to the conclusion that **D2** is not prejudicial to novelty, the invention claimed in claims 1 to 30 would have been obvious to the person skilled in the art in the knowledge of **D2** (optionally in conjunction with **D3** and **D4**) in the light of the general expert knowledge.

3.9 Claims 1-21 lack an inventive step compared with D7

3.9.1 Should document **D7** not be regarded as prejudicial to novelty contrary to

expectations, then the invention claimed in claims 1 to 21 would, however, in any case be obvious to the person skilled in the art in the knowledge of D7 in conjunction with the general expert knowledge.

3.10 Summary and conclusion

In the light of the general expert knowledge, all of the claims lack the required inventive step compared with the closest prior art.

V Insufficient disclosure (EPC Article 83)

1 The concentration ranges are insufficiently disclosed

1.1 The term "about", as used in claims 9-11 and 17-21, is not defined anywhere in the contested patent. Consequently, it is not possible for the person skilled in the art, without unreasonable effort, to determine whether a concentration does or does not lie within the claimed range. "About" could thus constitute +/- 0.05 mg/ml, +/- 5 mg/ml, or a percentage (e.g. +/- 20%) of a concentration.

1.2 In particular, the concentration range in claim 10 cannot be reproduced without unreasonable effort on account of the unclearly defined wording "from about 25 mg/ml".

2 The technical effect cannot be determined

2.1 It is an object of the patent to provide a parenteral formulation for CCI-779 in which CCI-779 has improved solubility as well as improved chemical and physical stability.

2.2 However, nowhere in the application does the person skilled in the art find adequate information, let alone a reliable test as to how the chemical or physical stability can be precisely tested. Even the few clues in the examples are imprecise. Thus, for example, it is not defined what several hours (Examples 4 to 9) means. In addition, Examples 5, 6, 7 and 9 merely make statements about the physical stability, but not about the chemical stability.

2.3 Moreover, further important clues regarding the storage conditions are missing, e.g. whether the solutions in the contested patent were stored in the

dark or in light, which can have a big effect particularly on the stability of CCI-779.

2.4 Even if such tests were given, the person skilled in the art would not be able to draw any conclusions without unreasonable effort since the person skilled in the art is not placed in a position, as a result of the inadequate teaching of the contested patent, of comparing his results with those of the examples. Finally, the results of the examples in the contested patent are only worded extremely vaguely.

3 The claimed invention does not include functioning embodiments

3.1 The claimed invention also includes embodiments in which the alcoholic solvent in the cosolvent concentrates, and also the alcoholic and the dilution solvent in the parenteral formulation may be polyethylene glycol 1000. As the textbook "Fiedler, Lexikon der Hilfsstoffe [Lexikon of auxiliaries]" (1996) (**D6**) reveals, however, polyethylene glycol 1000 is a wax in pure form. Even in mixtures with, for example, water as dilution solvent, there are viscosity limits which make it impossible for the person skilled in the art to carry out the claimed invention in its full scope (see D6, page 1211, left-hand column, lower table and the table on page 1212, top).

3.2 Furthermore, in the independent claims, the concentration of the antioxidant is not limited in terms of range. As has already been explained before under point IV 2.3, this leads to embodiments which do not allow the person skilled in the art to carry out the claimed invention without unreasonable effort in its full scope.

3.3 Furthermore, the lower limit of the concentration range of the CCI-779 in the cosolvent concentrate is lower than in the parenteral formulation. It is thus not possible for the person skilled in the art to dilute a cosolvent concentrate, which can comprise CCI-779 in a concentration of 0.05 mg/ml, to give a parenteral formulation in which CCI-779 is present in a concentration of at least 1 mg/ml. Contrary to this, the contested patent teaches:

> *"When CCI-779 is prepared as a cosolvent concentrate according to this invention, the concentrate can contain concentrations of CCI-779 from 0.05 mg/ml, from 2.5 mg/ml, from 5 mg/ml, from 10 mg/ml or from*

25 mg/ml up to approximately 50 mg/ml. The concentrate can be mixed with the diluent up to approximately 1 part concentrate to 1 part diluent, to give parenteral formulations having concentrations of CCI-779 from 1 mg/ml, from 5 mg/ml, from 10 mg/ml, from 20 mg/ml, up to approximately 25 mg/ml."

(Page 4, lines 8 to 12; emphasis added)

Accordingly, the preparation process described in the contested patent includes embodiments which do not work.

VI Summary and conclusions

1 Only the filing date of the contested patent applies as effective priority to the subject matter of claims 1, 2, 4, 5, 9-11, 13-17, 19-23 and 25-30.

2 Claims 1 to 26 are not novel over D2 and/or D7.

3 Claims 1 to 30 do not meet the requirement of EPC Article 56.

4 Finally, the contested patent does not allow the person skilled in the art to carry out the alleged invention without unreasonable effort over the entire claimed range (**T 435/91**) and is therefore insufficiently disclosed.

5 The granted claims thus do not correspond to the requirements of the EPC.

6 The aforementioned request to revoke the contested patent in its entirety is therefore substantiated.

Anlage 2

Priorität: 30. Juli 2002
Anmeldetag: 25. Juli 2003

Liste der zitierten Dokumente

D1: US 60/399,526, Priorität begründende Patentanmeldung des Streitpatentes.

D2: WO 01/97809 A2, veröffentlicht in 2001. (D7 im Prüfungsverfahren)

D3: US 5,530,006, veröffentlicht in 1996. (D3 im Prüfungsverfahren)

D4: US 5,516,770, veröffentlicht in 1996. (D1 im Prüfungsverfahren)

D5: US 5,616,588, veröffentlicht in 1997.

D6: Fiedler, H., *Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete*, Band 2, 4. Auflage, Seiten 1210 bis 1217, Editio-Cantor-Verlag, Aulendorf, Deutschland, 1996.

D7: GB 2 327 611 A, veröffentlicht in 1999. (D10 im Prüfungsverfahren)

D8: US 4,401,653, veröffentlicht in 1983.

D9: Podsypanina K. et al., *An inhibitor of mTOR reduces neoplasia and normalizes p70/S6 kinase activity in Pten$^{+/-}$ mice*, PNAS, Band 98, Nr. 18, Seiten 10320-10325, August 2001.

D10: WO 94/02136, veröffentlicht in 1993.

D11: Sweetana, S. und Akers M., *Solubility Principles and Practices for Parenteral Drug Dosage Form Development*, PDA Journal of Pharmaceutical Science & Technology, Band 50, Nr. 5, September 1996.

D12: Strickley, R. *Parenteral Formulations of Small Molecules Therapeutics Marketed in the United States (1999) Part I*, PDA Journal of Pharmaceutical Science & Technology, Band 53, Nr. 6, Seiten.324 bis 349, November 1999.

D13: Powell, M. et al. *Compendium of Excipients for Parenteral Formulations*, PDA Journal of Pharmaceutical Science & Technology, Band 52, Nr. 5, Seiten 238 bis 311, November 1999.

D14: Sorbera, L.A. et al. *CCI-779 Oncolytic mTOR Inhibitor*, Drugs of the Future, Band 27, Nr. 1, Seiten 7-13, Januar 2002.

D15: Wyeth Pharmaceuticals Inc., HIGHLIGHTS OF PRESCRIBING INFORMATION (TORISEL, temsirolimus), Philadelphia, USA, Mai 2007.

D16: DE 44 18 115 A1, veröffentlicht in 1994. (D9 im Prüfungsverfahren)

D17: Garber, K. *Rapamycin's Resurrection: A New Way to Target the Cancer Cell Cycle*, Journal of the National Cancer Institute, Band 93, Nr. 20, Seiten 1517-1519, Oktober 2001.

D18: Grünwald, V. et al., *Inhibitors of mTOR Reverse Doxorubicin Resistance Conferred by PTEN Status in Prostate Cancer Cells*, Cancer Research, Band 62, Seiten 6141-6145, 1. November 2002. (Zwischenliteratur)

D19: WO 2000/33878, erteilt als EP 1 137 439 B1, veröffentlicht in 2000.

European Patent No 1 553 940 B1
Application No 03771828.5
Wyeth
Opposition by Teva Pharmaceutical Industries Ltd

Statement of Grounds of Opposition including Facts and Arguments in Support

1. Grounds of Opposition

European Patent No 1 553 940 B1 ("the Patent") is opposed on the grounds that it lacks novelty and inventive step; and that it does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

2. Requests

The Opponents request that the Patent be revoked in its entirety. Should the Opposition Division be unwilling to grant this request on the basis of the written record, oral proceedings are requested.

3. List of References

The following documents are relied upon. A copy of each is enclosed in duplicate.

Ref 1: WO 01/97809 (cited as D7 in the ISR/IPER)

Ref 2: Podsypanina *et al*, "An Inhibitor of mTOR reduces neoplasia and normalizes p70/S6 kinase activity in Pten$^{+/-}$ mice", *Proc. Natl. Acad. Sci. USA*, 98, 10320-10325, Aug 28 2001

Ref 3: Dudkin *et al*, "Biochemical Correlates of mTOR Inhibition by the Rapamycin Ester CCI-779 and Tumor Growth Inhibition", *Clinical Cancer Research*, 7, 1758-1764, June 2001

Ref 4: Georger *et al*, "Antitumor Activity of the Rapamycin Analog CCI-779 in Human Primitive Neuroectodermal Tumor/Medulloblastoma Models as Single Agent and in Combination Chemotherapy", *Cancer Research* 61, 1527-1532, Feb 15 2001

Ref 5: "Solution Formulations" in *Pharmaceutical Preformulation and Formulation*, 2001, pages 196-210

Ref 6: Mendenhall, "Stability of Parenterals", *Drug Development and Industrial Pharmacy*, 10(8&9), 1297-1342 (1984)

Ref 7: GB 2 327 611 (cited as D10 in the ISR/IPER)

Ref 8: US 5,530,006 (cited as D3 in the ISR/IPER)

√Ref 9: Yu *et al* "mTOR, a novel target in breast cancer: the effect of CCI-779, an mTOR inhibitor, in preclinical models of breast cancer", *Endocrine-Related Cancer*, 8, 249-258, 2001

✓ Ref 10: Grünwald *et al* "Inhibitors of mTOR Reverse Doxorubicin Resistance Conferred by PTEN Status in Prostate Cancer Cells", *Cancer Research* 62, 6141-6145, Nov 1 2002

✓ Ref 11: US 5,516,770 (cited as D1 in the ISR/IPER)

4. Effective Dates of the Claims

The Patent was granted on 13 February 2008 based on European patent application 03771828.5 having a filing date of 25 July 2003, the application being derived from the international patent application PCT/US2003/023276, and claiming priority from US provisional patent application 60/399,526 filed on 30 July 2002.

4.1 Claims 16, 26 and 27-30

The feature that the surfactant is polysorbate 20 is not implicitly or explicitly disclosed in US 60/399,526. Claims 16, 26 and 27-30 of the Patent include the feature that the surfactant is polysorbate 20 as one of two or more alternatives.

Claims 16, 26 and 27-30 can therefore each be divided into the two separate embodiments, the embodiment including the feature that the surfactant is polysorbate 20 having the effective date of 25 July 2003 (filing date), and the embodiment in which the surfactant is other than polysorbate 20 having the effective date of 30 July 2002 (priority date).

4.2 Other Claims

In case it becomes relevant, it is pointed out that further claims of the Patent are not entitled to the priority date because the following features are not implicitly or explicitly disclosed in US 60/399,526:

- the solvent component of the cosolvent concentrate is dimethylacetamide or a parenterally acceptable solvent in general (the priority document refers only to an alcoholic solvent);
- the alcoholic solvent or diluent solvent is polyethylene glycol 600 or polyethylene glycol 1000;
- the antioxidant comprises from about 0.001 to 1.0% w/v of the cosolvent concentrate (the disclosure of the range of from 0.001 to 1.0% w/v at page 3, 22-23 of the priority document refers to the amount of antioxidant in the formulation rather than the cosolvent concentrate);
- the antioxidant comprises from about 0.0005 to 0.5% w/v of the formulation;
- the surfactant comprises from about 0.5 to about 10% w/v of the formulation;
- the solvent comprises from about 10% to about 90% w/v of the formulation.

5. Novelty

5.1 Claims 1, 3 and 4

Claim 1 lacks novelty over Ref 1. Claim 1 is directed to a CCI-779 cosolvent concentrate which comprises CCI-779, a parenterally acceptable solvent, and an antioxidant.

Ref 1 is directed to methods for treating certain diseases using a rapamycin, and products for use in such methods. The term "a rapamycin" is defined as the class of immunosuppressive compounds which contain the basic rapamycin nucleus (p.3, l.23-25). Ref 1 states that rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) is a particularly preferred member of this class of compounds (p.6, l.4-6).

Ref 1 discloses that the rapamycin may be administered in combination with an antioxidant (p.9, lines 17 and 25, and claim 31), that the combination may be administered as a unitary dosage form containing both components (p.10, l.8-9), and that such doses may be administered parenterally (p.10, l.14-16). Pharmaceutical forms for injectable use are mentioned (p.11, l.28) and, for such administration, a carrier such as water, ethanol, glycerol, propylene glycol and polyethylene glycol or mixtures thereof may be used (p.11, l.33-p.12, l.3).

Accordingly, since Ref 1 directly and unambiguously discloses all of the elements of claim 1, claim 1 lacks novelty over Ref 1.

Claim 3 also lacks novelty over Ref 1, since the additional feature that the parenterally acceptable solvent is an alcoholic solvent is also disclosed in Ref 1, since Ref 1 lists the alcohols ethanol, glycerol, propylene glycol and polyethylene glycol as suitable carriers (p.11, l.33-p.12, l.3).

Claim 4 also lacks novelty over Ref 1, since the additional feature that the alcoholic solvent comprises ethanol, propylene glycol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600 or polyethylene glycol 1000 is also disclosed in Ref 1 (p.11, l.33-p.12, l.3).

5.2 Claims 12, 13 and 15

Claim 12 lacks novelty over Ref 1. Claim 12 is directed to a parenteral formulation which comprises CCI-779, an alcoholic solvent, an antioxidant, a diluent solvent, and a surfactant.

Paragraph 5.1 above already shows that Ref 1 discloses a parenteral formulation comprising CCI-779, an alcoholic solvent and an antioxidant. Ref 1 also discloses that, for parenteral administration, solutions or suspensions of the active compounds in water

mixed with a surfactant can be prepared (p.11, 1.20-23), and mixtures of solvents are specifically disclosed (page 12 lines 2 to 3).

Accordingly, since Ref 1 directly and unambiguously discloses all of the elements of claim 12, claim 12 lacks novelty over Ref 1.

Claim 13 contains the same features as claim 4, and the statements made in section 5.1 apply. Accordingly, claim 13 also lacks novelty over Ref 1.

Claim 15 also lacks novelty over Ref 1, since the additional feature that the diluent solvent is water, ethanol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600 or polyethylene glycol 1000 or propylene glycol is also disclosed in Ref 1 (p.11, l.33-p.12, l.3)

6. Inventive Step

6.1 Claim 1

For the reasons given above in section 5.1, claim 1 lacks novelty. In addition, it is submitted that claim 1 lacks inventive step.

Considering inventive step for the invention using the so-called problem and solution approach favoured by the EPO Boards of Appeal, the situation can be analysed as follows.

6.1.1 Technical Problem as stated in the Patent

With regard to the drug cosolvent concentrate, which is the subject of claim 1, the problem in the formulation of CCI-779 in certain water-miscible organic solvents is chemical instability which, as indicated in the patent, can be due to oxidative degradation of CCI-779 or cleavage of a lactone bond, resulting in the formation of the ring-opened seco-CCI-779 (see Patent, p.2, paragraph 9, l.47-50).

According to the Patent, the presence of an antioxidant enhances the stability of CCI-779 (p.3, paragraph 17, l.28-29) and chelating agents are also capable of enhancing the stability of CCI-779 (p.3, paragraph 18, especially l.37-39).

6.1.2 Disclosure of Reference 2

Ref 2 is a report of the use of CCI-779 in the *Pten* +/- mouse tumour model system. Ref 2 discloses that CCI-779 is diluted to 50 mg/ml in 100% ethanol. This ethanolic solution of CCI-779 is then mixed with 5% Tween-80/5% polyethylene glycol-400 to a 2 mg/ml drug/ 4% ethanol final concentration (p.10320, column 2, paragraph headed "Mice and Treatment"). The solution is delivered to the mice intravenously i.e. parenterally.

Thus Ref 2 discloses a CCI-779 cosolvent concentrate which comprises CCI-779, and ethanol as a parenterally acceptable solvent. Similar cosolvent concentrates are also disclosed in Ref 3 (p.1759, column 1, paragraph headed "Tumor Growth and Measurement of Tumor Response") and Ref 4 (p.1527, column 2, paragraph headed "Drugs" and page 1528, column 1, paragraph headed Treatment with CCI-779 and/or Cisplatin), either of which could be used in place of Ref 2.

Ref 2 (or Ref 3 or Ref 4) thus discloses a known CCI-779 cosolvent concentrate which was being used by the skilled person at the priority date to prepare formulations of CCI-779 effective at delivering the drug into a mammal.

6.1.3 Formulation of the Objective Technical Problem starting from Reference 2

The CCI-779 cosolvent concentrate disclosed in Ref 2 contains all of the components of claim 1 except the antioxidant. Thus the difference between claim 1 and the disclosure of Ref 2 is that the CCI-779 cosolvent concentrate of claim 1 additionally comprises an antioxidant.

The technical effect of the inclusion of the antioxidant in the CCI-779 cosolvent concentrate as claimed in claim 1 is the enhancement of the stability of CCI-779 (see Patent, p.3, paragraph 17, l.28-29)).

Therefore, starting from Ref 2, the objective technical problem to be solved by the present invention is the provision of a CCI-779 cosolvent concentrate having enhanced stability.

6.1.4 Solution to the Objective Technical Problem can be found in the Common General Knowledge

The skilled person in the field of formulation chemistry would be aware that stability was essential when developing a commercial product. The general knowledge of such a skilled person would encompass known measures for stabilising active compounds in solution, including the use of antioxidants.

Such measures are described in many textbooks and other literature references in the technical field, for example the excerpts provided as Ref 5 and Ref 6. For example, in Ref 5, the use of antioxidants to protect active compounds from oxidation is described (page 203), suitable antioxidants being listed in Table 6.8; and the use of chelating agents is described on page 203, l. 7 and pages 206-208. Page 1319, l. 21-22 of Ref 6 states that

> "formulation approaches, such as antioxidants, are usually the first choice to enhance shelf-life of such products",

and suitable antioxidants and chelating agents available for use in aqueous or non-aqueous parenteral products are listed in Table 3 on page 1320.

Given the objective technical problem of stabilisation of a CCI-779 cosolvent concentrate, especially when it is considered that the instability issue involves oxidation, the skilled person would add an antioxidant to the solution disclosed in Ref 2, and arrive at the CCI-779 cosolvent concentrate of claim 1.

Therefore the solution to the technical problem provided by the present invention as claimed in claim 1 would have been obvious to the person skilled in the art using the teaching of Ref 2 in light of the common general knowledge.

6.1.5 Solution to the Objective Technical Problem can be found in Reference 7

Alternatively, the solution to the objective technical problem can be found in Ref 7.

Ref 7 is directed to the stabilisation of macrolide compositions, including compositions of rapamycin and its derivatives. Ref 7 teaches that rapamycin compositions can be stabilised using acid compounds, and preferred acids include citric acid (p.4, l.21-22). Example 5 of Ref 7 discloses a composition comprising the rapamycin analogue 40-O-(2-hydroxy)ethyl rapamycin, Cremophor EL, citric acid and ethanol. The Example demonstrates that citric acid has a stabilising effect on the rapamycin analogue. Ref 7 also teaches that the main degradation product of a rapamycin is the secorapamycin i.e. the ring-opened lactone form of the rapamycin, and that lactone cleavage is the main instability issue (p.6, l.8-9, and p.3, l.6-11).

The patentee has used the term "antioxidant" in the claims of the Patent. However, since the Patent suggests that the antioxidant component may have chelating activity, it appears to be the patentee's intention that the term "antioxidant" should encompass components that are chelating agents that also have antioxidant properties. In addition, the Patent specifically mentions citric acid as a preferred "antioxidant", and therefore citric acid is considered to fall within the scope of the term "antioxidant".

The skilled person looking for a suitable agent to stabilise a CCI-779 cosolvent concentrate would look at agents that are effective at stabilising solutions of rapamycin and other rapamycin anolgues, since he would expect the compounds to behave in an analogous manner. Indeed, as with the rapamycins discussed in Ref 7, the instability issue with CCI-779 was considered to involve lactone cleavage, resulting in the formation of the ring opened seco-CCI-779, as acknowledged by the patentee (see Patent, p.2, paragraph 9, l.49-50). Therefore the person skilled in the art aiming to stabilise CCI-779 would incorporate any one of the acid compounds, including citric acid, disclosed in Ref 7 as being effective at stabilising other rapamycins, into the solution of Ref 2, and he would arrive at a CCI-779 cosolvent concentrate falling within the scope of claim 1 without exercising any inventive activity.

Therefore the solution to the technical problem provided by the present invention as claimed in claim 1 would have been obvious to the person skilled in the art using the teaching of Ref 2 in combination with Ref 7.

6.2 Claim 2

Claim 2 (dependent on claim 1) specifies that the parenterally acceptable solvent is dimethylacetamide.

As mentioned in paragraph 5.1, Ref 1 is directed to methods for treating certain diseases using a member of the rapamycin class of compounds, of which CCI-779 is particularly preferred and may be administered parenterally. As shown, Ref 1 already discloses the combination of CCI-779 in combination with an antioxidant and a solvent carrier, the main difference between claim 2 and the disclosure of Ref 1 is that the CCI-779 in claim 1 is formulated as a cosolvent concentrate in dimethylacetamide.

There does not appear to be any technical effect associated with the use of dimethylacetamide in the CCI-779 cosolvent concentrate as claimed in claim 2.

Therefore, the objective technical problem to be solved is the provision of a specific formulation of CCI-779 using an alternative solvent to those mentioned in Ref 1. The solution to that problem can be found in Ref 8, which discloses an aqueous formulation of rapamycin for intravenous injection (iv) (column 1, l.7-8). The formulation comprises a concentrate solution of rapamycin in N,N-dimethylacetamide, in combination with a specific diluent (column 1, l.8-13).

The skilled person looking for a suitable means for formulating CCI-779 would inevitably consider those formulations already disclosed as being suitable for rapamycin. Indeed, Ref 1 states that preferred parenteral formulations include those disclosed in US 5,530,006 [Ref 8] (p.12, l.3-5). Thus, Ref 1 contains a clear and unmistakable reference to the disclosure of Ref 8.

Given the objective technical problem of providing a specific formulation of CCI-779 using an alternative solvent to those mentioned in Ref 1, the skilled person would use N,N-dimethylacetamide as disclosed in Ref 8, and arrive at the CCI-779 cosolvent concentrate of claim 2. Therefore the solution to the technical problem as claimed in claim 2 would have been obvious to the person skilled in the art using the teaching of Ref 1 in combination with Ref 8.

6.3 Claim 3

Claim 3 specifies that the parenterally acceptable solvent is an alcoholic solvent. As outlined above in section 6.1, Ref 2 already discloses ethanol, i.e. an alcoholic solvent, as the parenterally acceptable solvent component. Accordingly, claim 3 also lacks inventive step.

6.4 Claim 4

Claim 4 specifies that the alcoholic solvent is ethanol, propylene glycol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, or polyethylene glycol

1000. As outlined above in section 6.1, Ref 2 already discloses ethanol as the alcoholic solvent component. Propylene glycol and the various polyethylene glycols are other alcoholic solvents that are routinely used in parenteral formulations, and their use would be part of the common general knowledge and an obvious alternative to ethanol, so that claim 4 also lacks inventive step.

6.5 Claim 5

Claim 5 specifies that the antioxidant is citric acid, glycine, d,l-α-tocopherol, BHA, BHT, monothioglycerol, ascorbic acid, or propyl gallate. The common antioxidants and chelating agents used in parenteral formulations and concentrate solutions as components of such formulations would be within the common general knowledge of the skilled person. Such general knowledge is represented, for example, by Table 6.8 on page 203 of Ref 5, the description of chelating or complexing agents on pages 206-208 of Ref 5, and Table 3 on page 1320 of Ref 6. Thus the use of any of citric acid, d,l-α-tocopherol, BHA, BHT, monothioglycerol, ascorbic acid, or propyl gallate would be contemplated by the skilled person. The patentee has merely made an arbitrary selection from a limited number of possible antioxidants and chelating agents known to the skilled person. Accordingly, claim 5 also lacks inventive step.

6.6 Claim 6

Claim 6 specifies that the CCI-779 cosolvent concentrate comprises CCI-779, citric acid and dehydrated ethanol. As outlined above in section 6.1, Ref 2 already discloses 100% ethanol, i.e. dehydrated ethanol, as the alcoholic solvent component. As discussed above in section 6.5, the use of citric acid as an antioxidant/chelating agent in parenteral formulations is within the common general knowledge of the skilled person as represented, for example, by the description of chelating or complexing agents on pages 206-208 of Ref 5 (see especially page 208, l.15), and Table 3 on page 1320 of Ref 6. Accordingly, claim 6 also lacks inventive step.

6.7 Independent claim 7

Claim 7 specifies that the CCI-779 cosolvent concentrate comprises CCI-779, dehydrated ethanol, d,l-α-tocopherol, and propylene glycol. As outlined above in section 6.1, Ref 2 already discloses 100% ethanol, i.e. dehydrated ethanol, as the alcoholic solvent component. As discussed above in section 6.5, the use of d,l-α-tocopherol as an antioxidant in parenteral formulations is within the common general knowledge of the skilled person as represented, for example, by Table 6.8 on page 203 of Ref 5 (see especially the mention of citric acid at page 208, l.15), and Table 3 on page 1320 of Ref 6.

According to the Patent, the use of a combination of ethanol and propylene glycol rather than ethanol alone produces a less flammable product (see Patent, p.3, l.25-26). The skilled person would be well aware of the inherent flammability of ethanol and when optimising a commercial product, he would seek to reduce the flammability by replacing some or all of the ethanol with an alternative alcoholic solvent. As mentioned

in section 6.4, propylene glycol is an alcoholic solvent that is routinely used in parenteral formulations, and using it in place of some or all of the ethanol would be an obvious choice. Accordingly, the cosolvent concentrate claimed in claim 7 would be arrived at merely by routine optimization carried out by the skilled person with no inventive activity, and thus claim 7 also lacks inventive step.

6.8 Claim 8

Claim 8 specifies that the cosolvent concentrate of claim 7 further comprises citric acid. As discussed above (sections 6.5 and 6.6), the use of citric acid as an antioxidant/ chelating agent in parenteral formulations was common general knowledge. Accordingly, claim 8 also lacks inventive step.

6.9 Claim 9

Claim 9 specifies that, in the cosolvent concentrate, CCI-779 comprises from about 0.05 mg/ml to about 50 mg/ml. As outlined above in section 6.1, Ref 2 already discloses a 50 mg/ml solution of CCI-779 in 100% ethanol, which is within the claimed range specified in claim 9. Accordingly, claim 9 also lacks inventive step.

6.10 Claim 10

Claim 10 specifies that, in the cosolvent concentrate, CCI-779 comprises from about 25 mg/ml. No upper limit of the range is specified. Reference is made to the disclosure mentioned in section 6.9 above. Accordingly, claim 10 also lacks inventive step.

6.11 Claim 11

Claim 11 specifies that, in the cosolvent concentrate, the antioxidant comprises from about 0.001% to 1.0%w/v. Usual concentrations of the common antioxidants and chelating agents used in parenteral formulations, and in concentrate solutions as components of such formulations, would be within the common general knowledge of the skilled person. Such general knowledge is represented, for example, by Table 3 on page 1320 of Ref 6. Thus the skilled person would consider using concentrations, such as 0.05-0.075% d,l-α-tocopherol, 0.005-0.02% BHT, 0.1-1.0% thioglycerol, 0.02-1.0% ascorbic acid, or 0.005-0.02% propyl gallate, all of which fall within the claimed range specified in claim 11. Accordingly, claim 11 also lacks inventive step.

6.12 Independent claim 12

For the reasons given above in section 5.2, claim 12 lacks novelty. It is further submitted that claim 12 lacks inventive step.

6.12.1 Technical Problem as stated in the Patent

With regard to the parenteral formulation, which is the subject of claim 12, the specification states that the two problems are chemical instability (as discussed above),

and precipitation upon dilution of the CCI-779 formulation with aqueous infusion solutions or with blood (see Patent, p.2, paragraph 9, l.47-53).

According to the Patent, the presence of an antioxidant enhances the stability of CCI-779 (p.3, paragraph 17, l.28-29) and chelating agents are also capable of enhancing the stability of CCI-779 (p.3, paragraph 18, l.37-39). Precipitation of CCI-779 upon dilution with aqueous infusion solutions or blood is prevented through the use of a surfactant contained in the diluent solution (p.3, paragraph 20, l.49-50).

6.12.2 Disclosure of Reference 2

As mentioned above in section 6.1, Ref 2 discloses that CCI-779 is diluted to 50 mg/ml in 100% ethanol, then mixed with 5% Tween-80/5% polyethylene glycol-400 to a 2 mg/ml drug/ 4% ethanol final concentration, and thus discloses a parenteral formulation which comprises CCI-779, ethanol as alcoholic solvent, polyethylene glycol-400 and water as diluent solvents, and polysorbate 80 (Tween-80) as surfactant. Section 6.1 also shows that similar parenteral formulations used in various preclinical studies are also disclosed in Ref 3 and Ref 4, and either could be used in place of Ref 2.

6.12.3 Formulation of the Objective Technical Problem starting from Reference 2

The formulation disclosed in Ref 2 contains all of the components listed in claim 12 except the antioxidant. Since the formulation of Ref 2 contains a surfactant, the precipitation problem mentioned above in paragraph 6.12.1 has already been solved. Thus the difference between claim 12 and the disclosure of Ref 2 is that the formulation of claim 12 additionally comprises an antioxidant.

The technical effect of the inclusion of the antioxidant in the formulation as claimed in claim 12 is the enhancement of the stability of CCI-779 in solution (see paragraph 17 of the Patent).

Therefore, starting from Ref 2, the objective technical problem to be solved is the provision of a parenteral formulation of CCI-779 having enhanced stability as a solution. This is the same problem mentioned in connection with claim 1.

6.12.4 Solution to the Objective Technical Problem can be found in the Common General Knowledge or in D7

Paragraphs 6.1.4 and 6.1.5 above already show that, faced with the problem of stabilisation of a parenteral formulation of CCI-779, especially when it is considered that the instability issue involved oxidation, the skilled person would be led to add an antioxidant to the formulation disclosed in Ref 2, and he would thereby arrive at the formulation of claim 12 without exercising any inventive activity.

Therefore the solution to the technical problem provided by the present invention as claimed in claim 12 would have been obvious to the person skilled in the art using the

teaching of Ref 2 in light of the common general knowledge or using the teaching of Ref 2 in combination with Ref 7.

6.13 Claim 13

Claim 13 contains the same features as claim 4, and the statements made in section 6.4 regarding the disclosure of Reference 2 and common general knowledge apply. Accordingly, claim 13 also lacks inventive step.

6.14. Claim 14

Claim 14 contains the same features as claim 5, and the statements made in section 6.5 apply. Accordingly, claim 14 also lacks inventive step.

6.15 Claim 15

Claim 15 specifies that the diluent solvent is water, ethanol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, polyethylene glycol 1000, or propylene glycol. As outlined above, Ref 2 discloses a mixture of water and polyethylene glycol 400 as the diluent solvent. Other polyethylene glycols, polypropylene glycol or ethanol would be obvious alternatives to polyethylene glycol 400 and/or water since they are routinely used in parenteral formulations and have similar solubility properties. Accordingly, claim 15 also lacks inventive step.

6.16 Claim 16

Claim 16 specifies that the surfactant is polysorbate 20, polysorbate 80, a bile acid, lecithin, an ethoxylated vegetable oil, vitamin E tocopherol propylene glycol succinate, or polyoxyethylene-polyoxypropylene block copolymers. As outlined above, Ref 2 already discloses polysorbate 80 as the surfactant. In relation to the surfactant being an ethoxylated vegetable oil, Ref 9 can be used in place of Ref 2, since Ref 9 discloses a formulation comprising CCI-779, ethanol, Cremaphor and water. It would be obvious to the skilled person to contemplate alternative surfactants to polysorbate 80 or an ethoxylated vegetable oil, and the list provided in claim 16 is merely an arbitrary selection from a limited number of known surfactants used in parenteral formulations.

In relation to the surfactant being polysorbate 20, Ref 10 can be used in place of Ref 2, since, as shown in section 4.1 above, this embodiment of the claim has the filing date as effective date. Like Ref 2, Ref 10 describes the treatment of mice with CCI-779, but the surfactant Tween 20 is used in place of the Tween 80 surfactant used in Ref 2. Ref 10 discloses that CCI-779 is diluted in ethanol at a concentration of 50 mg/ml and then diluted to 2 mg/ml in 0.15M NaCl, 5% Tween 20, and 5% polyethylene glycol 400 (p.6142, column 1). The solution is delivered to the mice intraperitoneally, i.e. parenterally. Thus the technical difference between this embodiment of claim 16 and Ref 10 is the presence of an antioxidant, and therefore the objective technical problem is the same as for claim 12. The statements in section 6.12 regarding the common general knowledge and the disclosure of Ref 7 apply.

Accordingly, claim 16 also lacks inventive step over Ref 2, Ref 9 or Ref 10 in light of the common general knowledge, or in combination with Ref 7.

6.17 Claim 17

Claim 17 specifies that, in the formulation, CCI-779 comprises from about 1 mg/ml to about 25 mg/ml. As outlined above in section 6.12.2, Ref 2 already discloses a 2 mg/ml CCI-779 parenteral formulation, which is within the claimed range specified in claim 17. Accordingly, claim 17 also lacks inventive step.

6.18 Claim 18

Claim 18 specifies that, in the formulation, CCI-779 comprises from about 2.5 mg/ml to about 10 mg/ml. As outlined above in section 6.12.2, Ref 2 already discloses a 2 mg/ml CCI-779 parenteral formulation. The formulation of Ref 2 is used for administration of CCI-779 to mice in preclinical studies of the drug. It is within the common general knowledge of the skilled person that the amount of drug required by a patient is determined relative to their body weight, so that a human requires a much larger amount of a certain drug than a mouse. Thus, in order to improve handling and minimise the volume of solutions required when scaling-up a formulation for administration to a human, a more concentrated formulation is desirable. Accordingly, increasing the concentration of CCI-779 in the formulation from 2 mg/ml to the range of from about 2.5 mg/ml to about 10 mg/ml is merely standard workshop optimisation, and thus claim 18 also lacks inventive step.

6.19 Claim 19

Claim 19 specifies that, in the formulation, the antioxidant comprises from about 0.0005% to 0.5%w/v. This corresponds to the range of claim 11 after dilution in a ratio of 1:1. The concentration ranges exemplified in the common general knowledge reference, Reference 6, for d,l-α-tocopherol, BHT, thioglycerol, ascorbic acid and propyl gallate fall within or overlap with the claimed range specified in claim 19. Accordingly, claim 19 also lacks inventive step.

6.20 Claim 20

Claim 20 specifies that the surfactant comprises from about 0.5% w/v to about 10% w/v of the formulation. As mentioned above in section 6.1, Ref 2 discloses that CCI-779 is diluted to 50 mg/ml in 100% ethanol, then mixed with 5% Tween-80/5% polyethylene glycol-400 to a 2 mg/ml drug/ 4% ethanol final concentration (p.10320, column 2, paragraph headed "Mice and Treatment"). This corresponds to a 1:24 dilution ratio of concentrate to diluent, so that the amount of polysorbate 80 in the final formulation is 4.8%, which is within the range specified in claim 20. Accordingly, claim 20 also lacks inventive step.

6.21 Claim 21

Claim 21 specifies that the solvent comprises from about 10% to about 90% w/v of the formulation. It is not clear from the claim whether the solvent refered to is the alcoholic solvent, the diluent solvent or the combination of solvents, but it is assumed that the claim is intended to correspond to the statement on page 4, lines 19-20, so that the solvent refered to is the alcoholic solvent, i.e. the solvent in the cosolvent concentrate.

As discussed above (section 6.12.2), Ref 2 discloses a 2 mg/ml CCI-779/ 4% ethanol parenteral formulation, which is used for administration to mice. As mentioned previously (section 6.18), when scaling-up a formulation for administration to a human, the use of a more concentrated formulation improves handling, so that the use of a larger proportion of concentrate to diluent, and the resultant 10-90% w/v of solvent in the formulation, is merely standard workshop optimisation.

In addition, when determining the amount of solvent to be used, the skilled person would consider the amounts of solvents used in other known formulations comprising a concentrate and diluent. In particular, the skilled person would certainly consider rapamycin formulations such as those disclosed in Ref 11. Ref 11 discloses an aqueous formulation of rapamycin for intravenous injection (iv) (column 1, l.7-8). The formulation comprises a concentrate solution of rapamycin in propylene glycol, in combination with a specific diluent (column 1, l.8-13). The description of Ref 11 specifies that the propylene glycol comprises 5 to 30 weight % of the formulation (column 3, lines 29-37) and, in the Examples, a volume ratio of 1:5 concentrate to diluent is used, so that the amount of propylene glycol is approximately 17%. These amounts fall within or overlap with the claimed range of 10-90% w/v.

6.22 Independent claim 22

Claim 22 lacks inventive step. Claim 22 is directed to a process for preparing a parenteral CCI-779 formulation which comprises

(a) mixing CCI-779 with a parenterally acceptable solvent and an antioxidant component to provide a cosolvent concentrate;
(b) mixing a diluent solvent and a surfactant to produce a diluent; and
(c) mixing the cosolvent concentrate with the diluent to provide the CCI-779 parenteral formulation.

It is noted that processes in which a drug is mixed with a first solvent to make a concentrate, a surfactant is mixed with a second solvent to make a diluent, and subsequently the concentrate and diluent are mixed to provide the formulation are commonplace in the technical field of drug formulation. For example, both Ref 8 and Ref 11 describe such processes for preparing rapamycin formulations. Accordingly, there is nothing inherently inventive about the process itself.

As mentioned above in paragraphs 6.1.2 and 6.12.2, Ref 2 discloses a process in which CCI-779 is diluted to 50 mg/ml in 100% ethanol, then mixed with 5% Tween-80/5% polyethylene glycol-400 to a 2 mg/ml drug/ 4% ethanol final concentration (p.10320, column 2). Since the Tween-80 and polyethylene glycol-400 come from different suppliers, the step of mixing these reagents together with water to the required concentrations is implicitly disclosed. The solution is delivered to the mice intravenously, i.e. parenterally.

Thus Ref 2 discloses a process for preparing a parenteral CCI-779 formulation which comprises

(a) mixing CCI-779 with ethanol as parenterally acceptable solvent to provide a cosolvent concentrate;
(b) mixing polyethylene glycol-400 and water as diluent solvents and polysorbate 80 (Tween-80) as surfactant to produce a diluent; and
(c) mixing the cosolvent concentrate with the diluent to provide the CCI-779 parenteral formulation.

As shown in paragraph 6.1.2 above, similar processes for preparing parenteral formulations used in various preclinical studies are also disclosed in Ref 3 and Ref 4.

Ref 2 represents a known process for preparing a parenteral CCI-779 formulation which was being used by the skilled person at the priority date to prepare a formulation that was effective at delivering the drug into a mammal, the process containing all steps of the process of claim 22, except the inclusion of the antioxidant in mixing step (a). Thus the difference between claim 22 and the disclosure of Ref 2 is not a process step, but is the presence of an antioxidant as an additional component in mixing step (a), resulting in a formulation that includes an antioxidant. This difference is the same as that between claim 12 and the disclosure of Ref 2, and therefore the technical effect of this difference and the resulting objective technical problem to be solved is the same as that discussed above in relation to claim 12 (section 6.12.3).

Using the same reasoning as discussed in paragraph 6.12.4 and 6.12.5 in relation to claim 12, the solution to the technical problem as claimed in claim 22 would have been obvious to the person skilled in the art using the teaching of Ref 2 in light of the common general knowledge, or alternatively it would have been obvious using the teaching of Ref 2 in combination with Ref 7.

6.23 Claim 23

Claim 23 contains the same features as claim 4, and the statements made in section 6.4 apply. Accordingly, claim 23 also lacks inventive step.

6.24 Claim 24

Claim 24 contains the same features as claim 5, and the statements made in section 6.5 apply. Accordingly, claim 24 also lacks inventive step.

6.25 Claim 25

Claim 25 contains the same features as claim 15, and the statements made in section 6.15 apply. Accordingly, claim 25 also lacks inventive step.

6.26 Claim 26

Claim 26 contains the same features as claim 16, and the statements made in section 6.16 apply. Accordingly, claim 26 also lacks inventive step.

6.27 Claim 27

Claim 27 specifies that the solvent is dehydrated ethanol, the antioxidant is citric acid, the diluent solvents are water and polyethylene glycol 400, and the surfactant is polysorbate 20 or polysorbate 80. As outlined above in section 6.22, Ref 2 already discloses a process in which the solvent is 100% ethanol, i.e. dehydrated ethanol, the diluent solvents are water and polyethylene glycol 400, and the surfactant is polysorbate 80. An analogous process in which the surfactant is polysorbate 20 is disclosed in Ref 10 (see section 6.16). As discussed above (sections 6.5 and 6.6), the use of citric acid as an antioxidant/chelating agent in parenteral formulations was common general knowledge. Accordingly, claim 27 also lacks inventive step.

6.28 Claim 28

Claim 28 specifies that the solvent is dehydrated ethanol, the antioxidant is citric acid, the diluent solvents are dehydrated ethanol and polyethylene glycol 400, and the surfactant is polysorbate 20 or polysorbate 80. The components are the same as claim 27, except that the water in the diluent has been replaced with dehydrated ethanol. There appears to be no technical effect associated with the change of solvent, and this is merely an obvious workshop modification using an alternative solvent commonly used in parenteral formulations. Accordingly, claim 28 also lacks inventive step.

6.29 Claim 29

Claim 29 specifies that the solvents are dehydrated ethanol and propylene glycol, the antioxidant is d,l-α-tocopherol, the diluent solvents are water and polyethylene glycol 400, and the surfactant is polysorbate 20 or polysorbate 80. As outlined above in section 6.22, Ref 2 already discloses a process in which the solvent is 100% ethanol i.e. dehydrated ethanol, the diluent solvents are water and polyethylene glycol 400, and the surfactant is polysorbate 80. An analogous process in which the surfactant is polysorbate 20 is disclosed in Ref 10 (see section 6.16). As discussed above (section 6.7), the use of a combination of dehydrated ethanol and propylene glycol instead of ethanol alone in the cosolvent concentrate would be the result of routine optimization

carried out by the skilled person with no inventive activity. As discussed above (section 6.5), the use of d,l-α-tocopherol as an antioxidant in parenteral formulations is within the common general knowledge. Accordingly, claim 29 also lacks inventive step.

6.30 Claim 30

Claim 30 specifies that the solvents are dehydrated ethanol and propylene glycol, the antioxidant is d,l-α-tocopherol, the diluent solvents are dehydrated ethanol and polyethylene glycol 400, and the surfactant is polysorbate 20 or polysorbate 80. The components are the same as claim 29, except that the water in the diluent has been replaced with dehydrated ethanol. The statements in section 6.28 apply, and accordingly, claim 30 also lacks inventive step.

7. Sufficiency

The patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

The formulations described in the Examples are produced by mixing a cosolvent concentrate of Examples 1, 2 or 3 with the diluents of Examples 4-9. Examples 1, 2 and 3 all describe cosolvent concentrates including citric acid, the cosolvent concentrates of Examples 2 and 3 additionally including d,l-α-tocopherol. Examples 1, 2 and 3 all demonstrate various levels of satisfactory stability.

There is no data in the patent showing the level of stability of cosolvent concentrates without citric acid. The patent states that chemical instability of CCI-779 is noted in virtually all solvents (see paragraph 9, lines 3 to 7) and so, assuming that there are instability problems with CCI-779 in the solvents of Examples 1, 2 and 3, those examples illustrate only the stabilising effect of *citric acid* on CCI-779 in a cosolvent concentrate.

Citric acid is known to be a chelating agent (see for example Ref 6, pages 1319-1320, especially Table 3 on page 1320). This is also acknowledged by the patentee in paragraph 18 of the opposed patent. Thus citric acid is a compound exhibiting chelating activity as well as being an antioxidant. Other antioxidants (having no chelating activity) that are commonly used in parenteral formulations are listed, for example, on page 203 of Ref 5 and in Table 3, page 1320 of Ref 6.

every chelating agent is not an anti-oxidant or suitable for parenteral delivery

Thus the patentee has only provided Examples including a specific chelating agent that is also known to have antioxidant properties, specifically citric acid. The patentee has provided no example without citric acid, and thus no example of a formulation that only includes an antioxidant without chelating activity as the antioxidant component. Thus, all that has been demonstrated is that stabilised cosolvent concentrates and formulations may be produced by using citric acid. The technical effect of the inclusion of citric acid might be generalised to other chelating agents, but not to other antioxidants that do not have chelating activity. In this connection it is noted that the description of the Patent

no support

no basis to disregard argued effect of α-tocopherol as anti-oxidant → not a chelating agent

on page 2, lines 57-58 specifies that the problems (of instability etc) are avoided by the presence of an antioxidant and/or chelating agent in the solution.

Thus, since the patentee has only provided the skilled person with sufficient details to enable him to produce stabilised cosolvent concentrates and formulations using a chelating and antioxidant agent, rather than an antioxidant alone, the patent lacks sufficiency.

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11 November 2008

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June 18, 2009

VIA FACSIMILE (total 3 pages)
Confirmation by Air Mail

Attention: Ms. Cathy A. Kodroff

Your Ref: AM100802
Our Ref: P198045
Japanese Patent Application No. 2004-524806
Applicant: Wyeth

DOCKET
DUE DATE 8/26/09

Dear Ms. Kodroff:

Further to our letter of May 29, 2009, we provide you with an English translation of the Official Action and our comments. [redacted]

[redacted]

In the Official Action, the Examiner states as follows.

> *The following claims are rejected under the Patent Law, Article 29, Section 2 as being obvious over the following references.*

Claims 1-30 / Cited References 1-9

Cited References 1-3 disclose a parenteral formulation which comprising rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (hereinafter referred to as "CCI-779"), a surfactant such as polysorbate 80 or cremohpor EL (5-8%), and an alcoholic solvent such as ethanol, polyethylene glycol 400 (Cited Reference 1: page 10320, right column, lines 28-35; Cited Reference 2: page 250, right column, lines 16-32; Cited Reference 3: page 1759, left column, lines 14-28).

The invention claimed in claims 1-30 of the present application is different from the disclosures contained in Cited References 1-3 in that the claimed formulation contains 0.0005-0.5% of antioxidant, that the claimed formulation includes those which contains a surfactant other than the above surfactants disclosed in Cited References 1-3, that the

claimed formulation includes those which contains an alcoholic solvent other than the above alcoholic solvents disclosed in Cited References 1-3 and the concentration of the alcoholic solvent is 10-90%.

However, Cited Reference 5 describes that rapamycin and rapamycin derivative are unstable upon storage (page 14, line 15 to page 15, line 4 in WO 96/13273 corresponding to Cited Reference 5).. Cited Reference 4 describes that poly-ene macrolides including rapamycins are unstable to oxidation (Claims 1-13, page 1 in Cited Reference 4). Further, Cited Reference 6 describes that an antioxidant such as citric acid is added to prevent oxidative decomposition of a parenteral preparation, and the concentrations of antioxidants which are usually used are as follows: tocopherol 0.05-0.075%; BHT 0.005-0.02%; monothioglycerol 0.1-1.0%; Ascorbic Acid 0.02-1.0%; Propylgallate 0.005-0.02% (page 1319, line 6 to page 1323, line 12, Table 3 in Cited Reference 6). Additionally, Cited References 4 and 7-9 disclose polysorbate 20, polyoxyethylene-polyoxypropylene co-polymers, lecithins, vitamin E TPGS, etc. as a surfactant which can be used like polysorbate 80 and cremophor EL in injection, and propylene glycol, polyethylene glycol 300, etc. as an alcoholic solvent which can be used like ethanol, polyethylene glycol 400 in injection (WO 96/13273 corresponding to Cited Reference 5: page 10, line 12 to page 12, line 20; US 5,516,770 corresponding to Cited Reference 7: Claims 1-27, 2nd column, line 19 to 4th column, line 49, EXAMPLEs 1-3; WO 98/30205 corresponding to Cited Reference 8: Claims 1-24, pages 7-9; WO 99/45918 corresponding to Cited Reference 9: Claims 1-26, Examples 1-11).

Thus, those skilled in the art can readily expect that CCI-779 which is structurally similar to rapamycins disclosed in Cited References 4 and 5 is also unstable to oxidation, and thereby those skilled in the art can readily add an antioxidant as disclosed in Cited Reference 6 at the above concentration to a parenteral preparation comprising CCI-779 disclosed in Cited References 1-3. Further, those skilled in the art can readily use the above surfactants and alcoholic solvents as disclosed in Cited References 4 and 7-9 which can be used like the above surfactants and alcoholic solvents as disclosed in Cited References 1-3 as substitute for them, and optimize an amount of an alcoholic solvent to be contained to around an amount of an alcoholic solvent to be contained disclosed in Cited References 1-3.

Further, it is not recognized that the invention claimed in claims 1-30 has particularly remarkable effects which those skilled in the art cannot expect.

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7. JP-A-7-149624 (corresponding to US 5,516,770)
8. JP-A-2001-508445 (corresponding to WO 98/30205)
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[Prior Art Documents which do not constitute the reasons for rejection]
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